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# Effects of Normobaric Hyperoxia in Traumatic Brain Injury: A Randomized Controlled Clinical Trial

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**Abstract**

**Background:** Traumatic brain injury (TBI) is one of the important causes of morbidity and mortality throughout the world, especially in young people. In recent years normobaric hyperoxia has become an important and useful step for recovery and improvement of outcome in TBI.

**Objectives:** The purpose of this study was to evaluate the effects of normobaric hyperoxia on clinical neurological outcomes of patients with severe traumatic brain injuries. We used the Glasgow outcome scale (GOS), barthel index, and modified rankin scale (mRS) to measure the outcomes of patients with TBI.

**Patients and Methods:** Sixty-eight consecutive patients with severe TBI (mean Glasgow coma scale [GCS] score: 7.4) who met the inclusion criteria were entered in this randomized controlled clinical trial. The patients were randomized into two groups, as follows: 1) experimental: received 80% oxygen via mechanical ventilator in the first 6 hours of admission, 2) control: received 50% oxygen by mechanical ventilator in the first 6 hours of admission and then standard medical care. We measured the GOS, Barthel Index, and mRS at the time of discharge from hospital and reassessed these measurements at the 6-month follow-up after injury.

**Results:** According to our study, there were no significant sex or age differences between the two groups (P = 0.595 and 0.074). The number of days in the intensive care unit (ICU) in the control group and experimental group were 11.4 and 9.4 days, respectively (P = 0.28), while the numbers of days of general ward admission were 13.9 and 11.4 days (P = 0.137) respectively. The status of GOS at time of discharge were severe = 13 and 10, moderate = 16 and 19, and low = 5 and 5 in the control and experimental groups, respectively (P = 0.723); 6 months after injury, the scores were as follows: moderate = 16 and 9, low = 15 and 25, and severe = 3 and 0 (P = 0.024). The Barthel index scores in the control and experimental groups were 59.7 and 63.9 at time of discharge (P = 0.369) and 82.7 and 91.3 at 6 months after injury (P = 0.018), respectively. The mRS results were 2.6 and 2.3 at time of discharge (P = 0.320) and 1.6 and 0.7 at 6 months after injury (P = 0.006) for the control and experimental groups, respectively.

**Conclusions:** According to the results of this study, oxygen therapy by mechanical ventilator in the first 6 hours after injury in patients with severe TBI can improve the final GOS, Barthel index, and mRS scores. It could also improve long-term outcomes and enhance rehabilitation and the quality of life.

*Keywords:* Brain Injuries, Oxygen Inhalation Therapy, Hyperbaric Oxygenation, Glasgow Outcome Scale

## 1. Background

Traumatic brain injury (TBI) is a common health problem with a significant effect on quality of life (1). The prevalence of head injury is about 0.56% of the US population, with a mortality rate of about 40% for severe head trauma. In the United States, 2% of the population lives with long-term disabilities following head injuries (2).

Neurocritical care in moderate and severe TBI patients is aimed at restoring and maintaining the normal physiology of the body. Most studies have shown that cerebral ischemia is a major reason of disability in TBI, but some have challenged this finding. In most studies, management has focused on improving cerebral perfusion and blood flow. In TBI, the $O_2$ context differs according to diffusion alterations at many different stages from the capillaries to the cell and then to the mitochondria (3).

Neuroprotective interventions, including intracranial pressure (ICP) and cerebral artery filling pressure (CPP) management, as well as oxygen therapy, improved the clinical outcomes of patients with stroke and head trauma (4, 5). An increased metabolism of neurons has been shown after brain injury (6). Due to an increased rate of ion transportation after neuron injury, there is an increased need for glucose, which is usually supplied through glycogenolysis in astrocytes (7). In contrast, tissue hypoxia after trauma shifts the glucose metabolism to the anaerobic pathway. The anaerobic metabolism of

glucose produces lactate, which is useless in the damaged mitochondria of injured neurons (8-10). Hence, oxygen therapy might increase damaged tissue oxygenation, initiate the aerobic pathway, and save neurons from death (11-13).

Following the observation of mitochondrial dysfunction in TBI and the use of brain tissue oxygen tension ($PbtO_2$) monitoring, most recent studies have focused on using hyperoxia to decrease the impact of TBI (14). Normobaric oxygen therapy is the therapeutic administration of a high level of oxygen at environmental pressures at 1 atmosphere absolute (ATA), which can easily be achieved via mechanical ventilators; this has been one of the important and useful steps for recovery and outcome improvement in TBI in recent years (3). However, significant controversy has arisen regarding this treatment because of contradictory clinical results (6, 11, 15). This variability may be partly due to methodological differences in evaluating the metabolic response to the hyperoxic challenge or the clinical and pathophysiological heterogeneity among TBI patients.

## 2. Objectives

The aim of this study is to assess the effects of normobaric hyperoxia on clinical neurological outcomes of patients with severe TBIs. We used the Glasgow outcome scale (GOS), Barthel index, and modified rankin scale (mRS) to measure the outcomes of TBI patients.

## 3. Patients and Methods

In this double blind clinical trial, we enrolled all patients with severe TBI who were admitted to the emergency ward of Besat hospital, Hamadan, Iran, in 2014. The study was reviewed and approved by the ethics committee of Hamadan University of Medical Sciences. The study protocol was explained to the patients, and the participants were asked to complete written informed consent form.

Sixty-eight patients were divided in two groups, namely the control group and experimental group. After endotracheal intubation, all patients who met the inclusion criteria were connected to a mechanical ventilator. In the experimental group, patients received 80% oxygen by mechanical ventilator in the first 6 hours after the traumatic accident (n = 34); in the control group, patients received 50% oxygen by mechanical ventilator in the first 6 hours after the traumatic accident (n = 34). There were no differences in the mechanical ventilators of the patients, which were randomly allocated to the two groups. The patients were admitted to the intensive care unit (ICU), monitored carefully by expert nurses, and received standard medical care. The patients were examined for neurological defects at the time of discharge and in follow-up examinations were repeated 6 months after admission to hospital. To examine neurological defects, we used the Glasgow coma scale (GCS), Barthel index, and mRS neurologic disability scoring systems. The inclusion and exclusion criteria were as follows:

Inclusion criteria:

- Age between 18 and 65 years;
- Less than 6 hours passed since the accident;
- Hemodynamic stability; and
-GCS between 3 and 8.

Exclusion criteria:

- Pregnancy;
- Patients under 18 or older than 65 years;
- GCS under 3 or more than 8;
- Patients with chronic disease such as diabetes mellitus, ischemic heart disease, renal failure, acute pulmonary edema, history of massive myocardial infarction, and heart failure;
- Patients with a baseline blood pressure of less than 90/60;
- Patients with successful cardiopulmonary resuscitation (CPR);
- Death or loss to follow-up;
- Patients in the control group in which oxygen therapy was inevitable was also excluded from this study.

The sample size was calculated according to the findings of previous studies (16). Data were analyzed using STATA software version 11. An independent student's t-test was used to compare the parametric variables between the two groups, and a Chi-square test was also used. Mean data are represented as the mean ± standard deviation (SD). P values less than 0.05 were considered significant.

## 4. Results

In our study, 68 TBI patients were admitted to our emergency medical service (EMS) during the study period. In the control group, 11 (32.4%) were female and 23 (67.6%) were male; in the experimental group, 9 (26.5%) were female and 25 (73.5%) were male (P = 0.595). There was no statistically significant difference in age between the two groups (P = 0.074). The mean GCS scores in the control and experimental groups were 7.4 ± 0.89 and 7.4 ± 0.79, respectively (P = 0.773; Table 1).

The length of stay in the ICU in the experimental group was 11.4 days, while it was 9.4 days in the control group (P = 0.281). There were no statistically significant differences in length of stay in the general ward between two groups (P = 0.137).

The Barthel index exhibited no statistically significant differences between the two groups at the time of discharge (P = 0.369), but there was a statistically significant difference at 6 months after the event (P = 0.018). According to the mRS, there was no difference between the patients in the groups at the time of discharge (P = 0.320); however, after treatment (after 6 months), there were significant difference between the mRS scores of the treated group and the controls (P = 0.001). The higher mRS scores of the patients treated with normobaric oxygen represented better outcomes of these patients compared to the controls (Table 2).

**Table 1.** Demographic and Clinical Characteristics of the Intervention Group (Receiving 80% Oxygen) and Control Group (Receiving 50% Oxygen)

| Variables | Control (n = 34) | Intervention (n = 34) | P Value |
|---|---|---|---|
| **Gender**[a] | | | 0.595 |
| Female | 11 (32.4) | 9 (26.5) | |
| Male | 23 (67.7) | 25 (73.5) | |
| **Age**[b] | 45.7 (13.3) | 39.7 (14.1) | 0.074 |
| **GCS**[b] | 7.4 (0.89) | 7.4 (0.79) | 0.773 |

[a]Values are expressed as No. (%).
[b]Values are expressed as mean (SD).

**Table 2.** Comparison of the Effect of Intervention Versus Control on Length of Stay, Barthel Index, and Modified Rankin Scale[a]

| Variables | Control (n = 34) | Intervention (n = 34) | P Value[b] | P Value[c] |
|---|---|---|---|---|
| **Duration of admission, d** | | | | |
| ICU | 11.4 (8.4) | 9.4 (6.6) | 0.281 | NA |
| Hospital | 13.9 (8.1) | 11.4 (5.4) | 0.137 | NA |
| **Barthel Index** | | | | |
| At discharge | 59.7 (19.1) | 63.9 (19.7) | 0.369 | 0.280 |
| After 6 months | 82.7 (15.8) | 91.3 (13.1) | 0.018 | 0.001 |
| **Modified Rankin Scale** | | | | |
| At discharge | 2.6 (1.3) | 2.3 (1.2) | 0.320 | 0.134 |
| After 6 months | 1.6 (1.3) | 0.7 (1.1) | 0.006 | 0.001 |

Abbreviation: NA, not available.
[a]Values are expressed as mean (SD).
[b]T-test, adjusted for age, gender, and baseline GCS.
[c]Analysis of variance.

**Table 3.** Comparison of the Effect of Hyperoxia in on the GOS the Experimental Versus Control Groups[a]

| GOS | Control (n = 34) | Intervention (n = 34) | P Value |
|---|---|---|---|
| **At discharge** | | | 0.723 |
| Low | 5 (14.7) | 5 (14.7) | |
| Moderate | 16 (47.1) | 19 (55.9) | |
| Severe | 13 (38.2) | 10 (29.4) | |
| Persistent | 0 (0.0) | 0 (0.0) | |
| **After 6 months** | | | 0.024 |
| Low | 15 (44.1) | 25 (73.5) | |
| Moderate | 16 (47.1) | 9 (26.5) | |
| Severe | 3 (8.8) | 0 (0.0) | |
| Persistent | 0 (0.0) | 0 (0.0) | |

[a]Values are expressed as No. (%).

There was no difference in GOS between two groups at the time of discharge from hospital (P = 0.723), but there was a statistically significant difference between two groups 6-month after the event (P = 0.024; Table 3).

## 5. Discussion

This study was undertaken to evaluate the effects of normobaric hyperoxia in patients with severe TBI. According to the results of our study, oxygen therapy with the mechanical ventilator in the first 6 hours after tracheal intubation in severe TBI patients can improve the final GOS, Barthel Index, and mRS; this could also improve the long-term outcomes of these patients.

The GOS applies to patients with brain damage and allows for the objective assessment of their recovery in five categories. This allows a prediction of the long-term course of rehabilitation to return to work and everyday life.

The Barthel scale or Barthel activities of daily living (ADL) index is an ordinal scale used to measure performance in ADL. Each performance item is rated on this scale with a given number of points assigned to each level or ranking. It uses 10 variables describing ADL and mobility.

The mRS is a commonly used scale for measuring the degree of disability or dependence in people's daily activities when they have suffered a stroke or other causes of neurological disability. The scale runs from 0 - 6, spanning from perfect health without symptoms to death.

The normobaric hyperoxia detected could be reflective of the therapeutic intervention associated with major trauma (17). A high mortality rate in severe TBI patients has been reported in several studies; Raj et al. reported a mortality rate of about 39%, while in the Rockswold et al. study it was 42% (17, 18). However, for Raj et al. the addition of hyperoxia resulted in a significant relative risk reduction for mortality (17), as was found in other published studies (19, 20).

It has been demonstrated that normobaric hyperoxia is beneficial in the management of brain edema, control of intracranial pressure, and maintenance of cerebral perfusion pressure. Maintaining cerebral oxygenation levels at > 20 to 25 mmHg has resulted in decrease mortality rates and improved clinical outcomes. The risk of low brain oxygen is most acute in the first 24 to 48 hours after injury. The administration of oxygen with high $FIO_2$ (0.6 to 1.0) for the TBIs in the emergency room can be affective until patients are admitted to ICU for the placement of invasive neurocritical care monitoring systems. Therefore, the fraction of inspired oxygen levels needs to be titrated to prevent low brain oxygen levels (21-24).

Penumbra protection is one of the other main theories concerning the beneficial effects of oxygen therapy. Those injured brain areas that are ischemic as a result of the trauma are referred to as the "ischemic penumbra." This is the surrounding area around the central core of dead (infracted) cells. These tissues do not receive enough oxygen for normal function but do receive enough to stay alive. These brain cells have been described as "stunned," "hibernating," or "sleeping" neurons (25, 26). Oxygen may resuscitate stunned neurons of the penumbra and inhibit ischemia and neural damage (27-29).

As a result of the lack of adenosine triphosphate (ATP) formation due to the lack of oxygen and nutrients, formation of new capillaries does not occur. Due to impaired neovascularization, the ischemic penumbra remains ischemic; as a result, an extensive amount of brain tissue remains ischemic and non-functioning in the chronic stroke (27, 30). In contrast, prolonged oxygen therapy is accompanied by oxygen intoxication and adverse effects of prolonged oxygen therapy on lungs (31). Atelectesia, ventilation perfusion mismatch, pulmonary edema, and inflammation are among the known undesirable effects of oxygen therapy. However, the toxic effects of short periods of hyperoxia either normobaric or > 1 ATA have not been proven. Recent studies on $HBO_2$ by Rockswold et al. have shown that $HBO_2$ at 1.5 ATA for 60 minutes does not appear to produce $O_2$ toxicity and is considered safe in TBI (18, 32).

Larger studies are warranted to confirm our findings. These could separately compare the clinical outcomes of TBI patients after oxygen therapy. In conclusion, according to the results of this study normobaric oxygen therapy in the first 6 hours after accident can improve the outcomes of patients with head trauma.

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## Footnotes

**Authors' Contribution:**Abbas Taher developed the hypothesis, wrote the protocol, performed the study, and wrote the final report. Zahra Pilehvari performed literature review, collected the data, and wrote the final report. Jalal Poorolajal wrote the protocol, performed the data analysis, and wrote the final report. Mashhood Aghajanloo wrote the protocol and collected the data.

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