Evaluation of the Effect of Glibenclamide in Patients With Diffuse Axonal Injury Due to Moderate to Severe Head Trauma

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Abstract

Background: Traumatic brain injury (TBI) is a major health problem worldwide. Secondary injuries after TBI, including diffuse axonal injury (DAI) often occur, and proper treatments are needed in this regard. It has been shown that glibenclamide could reduce secondary brain damage after experimental TBI and improve outcomes.

Objectives: We aim to evaluate the role of glibenclamide on the short-term outcome of patients with DAI due to moderate to severe TBI.

Patients and Methods: In this controlled randomized clinical trial, 40 patients with moderate to severe TBI were assigned to glibenclamide (n = 20) and control (n = 20) groups. Six hours after admission the intervention group received 1.25 mg glibenclamide every 12 hours. The Glasgow coma scale (GCS) was administered at admission, in the first 24 and 48 hours, at one week post-trauma and at discharge. The Glasgow outcome scale (GOS) was also administered at discharge. All results were evaluated and compared between groups.

Results: Patients treated with glibenclamide compared to the control group had a significantly better GCS score one week post-trauma (P = 0.003) and at discharge (P = 0.004), as well as a better GOS score at discharge (P = 0.001). The glibenclamide group also had a shorter length of hospital stay compared to the control group (P = 0.03). In the control group, two patients (10%) died during the first week post-trauma, but there was no mortality in the glibenclamide group (P = 0.48).

Conclusions: Treatment with glibenclamide in patients with DAI due to moderate to severe TBI significantly improves short-term outcomes.

Keywords: Diffuse Axonal Injury, Traumatic Brain Injury, Glibenclamide, Outcome

1. Background

Traumatic brain injury (TBI) is a major health problem worldwide. Of TBI patients admitted to trauma centers, 15% have severe TBI with a higher mortality rate than other injuries (1-4). For patients who survive the initial injury, morbidity and mortality is often determined by secondary injury processes, which are both clinically apparent and currently underappreciated. TBI induces a plethora of structural and functional alterations, such as altered glucose uptake (5) and impaired glucose metabolism (5-7), which may cause secondary insults after TBI including edema, excitotoxicity, calcium accumulation, cell death cascades, axonal injury, altered cerebral blood flow, increase in oxidative species and enhanced inflammation (8).

There is a need for therapies that could prevent these secondary insults and improve the status of patients with TBI. Glibenclamide is a second-generation sulfonylurea, which is used as an oral hypoglycemic agent (9). It has been shown that glibenclamide has pleiotropic protective effects in acute central nervous system (CNS) injury. Several experimental studies have found that glibenclamide could be an effective treatment in various CNS pathologies including traumatic brain injury (10, 11) and spinal cord injury (12-15). It has been demonstrated that glibenclamide treatment administered shortly after injury is highly effective in reducing the pathological sequelae of TBI (10) and reduces secondary brain damage after experimental TBI (16).

However, there are few clinical studies that have evaluated the role of glibenclamide on TBI with promising results, such as improvement in the Glasgow coma scale (GCS) and the Glasgow outcome scale (GOS) at discharge (17).
2. Objectives

In this study, we evaluated the role of glibenclamide on the short-term outcome of patients with diffuse axonal injury (DAI) due to moderate to severe TBI.

3. Patients and Methods

In this randomized clinical trial, 40 patients with head trauma and diagnosis of diffuse axonal injury who were admitted to the neurosurgery ICU were evaluated. Patients over 18 years old who were admitted to the ICU during the first 24 hours after a close head injury, who had no bleeding in need of surgical intervention, had a GCS ≤ 12, and blood glucose > 125 were included. Patients with ICU period of less than 48 hours, chronic systemic diseases, BS < 80 mg/dL or > 300 mg/dL at any period were excluded. Patients who had used a sulphonylurea during the 30 days before the injury were also excluded. The protocol was approved by the institutional review board for Urmia University of Medical Sciences, and informed consent was obtained from all patients.

The study is powered to detect an effect size of $d \geq 0.70$ as statistically significant in a two-tailed test with $\alpha = 0.05$ and a power of 0.80 with $N = 20$. Sample size calculation was performed using G*power 3.1.9.2 software. Using RANDLIST 1.2 software, random numbers were produced, and according to sample size, patients were enrolled into the study. Patients were randomly assigned to intervention and control groups. Six hours after admission, the intervention group received 1.25 mg glibenclamide every 12 hours. The dose was increased to 2.5 mg/l2 hours if there was no hypoglycemia. The medication was given until the patient’s discharge from the ICU or for one week. Patients who had BS > 300 mg/dL were treated with insulin and excluded from the study. Blood sugar was checked by glucometry every two hours to detect and treat hypoglycemia.

The Glasgow coma scale (GCS) was measured in all patients at admission, in the first 24 hours, 48 hours, one week after admission and at discharge. The enhancement in GCS was measured using functional brain tests. The neurological outcome at discharge was evaluated using GOS. The GOS ratings are: 5 = good recovery, 4 = moderate disability, 3 = severe disability, 2 = persistent vegetative status, and 1 = death.

3.1. Data Analysis

All data were analyzed using the statistical package for social sciences, version 17.0 (SPSS, Chicago, Illinois). Baseline data are reported as mean ± standard deviation (continuous data) or percentages (categorical data), depending on the data level. The association between qualitative variables was studied using the Chi-square test or Fisher’s exact test. A P Value of 0.05 or less was considered significant.

4. Results

In this study, 40 patients with DAI due to TBI were evaluated in two groups; those treated with glibenclamide (n = 20) and a control group (n = 20). Table 1 shows the baseline findings between the groups. There was no significant difference between the groups. There were only two female patients with TBI. Most patients had GCS ≤ 8 at admission. All patients tolerated the medication and no cases of hypoglycemia were observed.

| Table 1. Baseline Findings Between Groups* |
|------------------------------------------|
|                                           |
| **Glibenclamide Group (n = 20)**          |
| **Control Group (n = 20)**                |
| **P Value**                               |
| **Age, y (mean ± SD)**                    | 31.15 ± 10.33 | 30.40 ± 13.16 | 0.84 |
| **Gender**                                |
| Male                                     | 18 (90)       | 20 (100)      | 0.48 |
| Female                                   | 2 (10)        | 0             |     |
| **GCS**                                   |
| 9 - 12                                   | 1 (5)         | 0             |     |
| 3 - 8                                    | 19 (95)       | 20 (100)      |     |

Abbreviations: GCS: Glasgow coma scale.

*Values are expressed as No. (%) unless otherwise indicated.

GCS data during the time and GOS data at discharge are shown in Table 2. Patients treated with glibenclamide had significantly better GCS one week post-trauma and at discharge, as well as better GOS at discharge compared to the control group.

Two patients (10%) died during the first week post-trauma in the control group, but no death was seen in glibenclamide group (P = 0.48). The length of hospital stay in the glibenclamide group was 15.65 ± 5.37 days, which was significantly lower than the control group (24.75 ± 18.29 days, P = 0.03).

5. Discussion

After TBI, secondary injury can occur in hours or days due to cellular damage secondary to TBI. Hypoxia, hypotension, increased intracranial pressure and brain edema are some of these complications (1). Although in recent years knowledge regarding the pathophysiological mechanisms of TBI has increased, there has been no great progress in therapeutic and medical treatments (1).
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Table 2. GCS During the Time and GOS at Discharge

|                        | Glibenclamide Group (n = 20) | Control Group (n = 20) | P Value |
|------------------------|-----------------------------|------------------------|---------|
| GCS after 24 hours post-trauma |                             |                        |         |
| 3 - 8                  | 19 (95)                     | 1 (5)                  | -       |
| 9 - 12                 | 19 (95)                     | 1 (5)                  | 0.69    |
| GCS after 48 hours post-trauma |                             |                        |         |
| 3 - 8                  | 15 (75)                     | 5 (25)                 |         |
| 9 - 12                 | 17 (85)                     | 3 (15)                 |         |
| GCS after 1 week post-trauma |                             |                        | 0.003*  |
| 3 - 8                  | 2 (10)                      | II (61)                |         |
| 9 - 12                 | 9 (45)                      | 5 (27.8)               |         |
| 12 - 15                | 9 (45)                      | 2 (11.1)               |         |
| GCS at discharge       |                             |                        |         |
| 3 - 8                  | 0                           | 3 (16.7)               | -       |
| 9 - 12                 | 0                           | 4 (22.2)               |         |
| 12 - 15                | 20 (100)                    | II (61)                |         |
| Mean GCS at discharge  | 13.95 ± 0.82                | 11.50 ± 3.43           | 0.004*  |
| GOS at discharge       |                             |                        |         |
| 1 - 3                  | 0                           | 9 (45)                 | 0.004*  |
| 3 - 5                  | 20 (100)                    | II (55)                |         |
| Mean GOS at discharge  | 4.70 ± 0.47                 | 3.40 ± 1.50            | 0.004*  |

Abbreviations: GCS, glasgow coma scale; GOS, glasgow outcome scale.
*P is two-sided significant.

In animal studies, it has been shown that glibenclamide reduces brain edema and contusion volume after experimental TBI (10). Ahmed, in a study of seven patients, including two patients with TBI, observed that glibenclamide is effective in controlling cerebral edema from different etiologies (18). Kimberly et al. (19) also reported reduced vasogenic edema following treatment with IV glyburide (glibenclamide) in stroke patients.

There are few previous studies as clinical trial regarding glibenclamide effects on CNS injuries, especially TBI (17); and there is one ongoing phase II clinical trial evaluating the effect of an intravenous formulation of glibenclamide in patients with TBI (20). However, most experimental studies on animals have shown great potency for glibenclamide in preventing and reducing secondary injuries after TBI and other CNS disorders (10-15).

In this prospective randomized clinical trial we evaluated the effect of glibenclamide on the short-term outcome of patients with DAI due to moderate to severe TBI. We observed significant improvement in GCS and GOS at discharge, following glibenclamide treatment compared to the control group. Similarly, Sheth et al. (21) observed better clinical outcomes in patients treated with glyburide (glibenclamide) for injection compared to controls. However, Ding and colleagues (17) observed no significant effect of glibenclamide on the outcomes of TBI patients with diabetes mellitus type 2, including changes in GCS and GOS, at discharge.

It is well known that an increase in hospital stay is accompanied by various complications including pneumonia. So, reducing the hospital stay is important in many clinical situations. Among outcome indicators evaluated in this study, we observed significant reduction in hospital length of stay in patients treated with glibenclamide compared to the control group. Similarly, Ding and colleagues (17) observed that glibenclamide could reduce length of stay in the neurologic intensive care unit.

The mortality rate in severe TBI is almost 30% (2). So, it is important to define treatments that could reduce the morbidity and mortality rate, as well. It has been shown that treatment with glibenclamide reduces mortality in brain injury models (22, 23). Simard and colleagues (24), in a study on rats, observed that the mortality following glibenclamide treatment was significantly reduced in the first day post-trauma in experimental TBI models. In our clinical trial, we observed no mortality in patients receiving glibenclamide and only two deaths (10%) in the control group. Although the difference between the groups was not significant, it is clinically important to observe a reduced mortality rate.

The present study has several limitations. First, the sample sizes for each group might be too small to make a general statement regarding the results. However, this is one of the few studies performed in this regard as a clinical trial, and not on animals, so the results could be very promising. In addition, we only evaluated short-term outcome of treatment with glibenclamide and the long-term outcome is not clear. Also, the chronic use of glibenclamide after discharge could have some other benefits due to its interactions in the brain, which needs further studies.

In conclusion, treatment with glibenclamide in patients with moderate to severe TBI significantly improves GCS and neurological outcome at discharge, as well as length of hospital stay.
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Footnotes

Authors’ Contribution: Developing the original idea and the protocol, Firooz Salehpour; abstracting and analysis of data, Peyman Zafardoost; definition of intellectual content, Amir Abbas Ghasemi; manuscript review, Ehsan Ziaei; contribution to the development of the protocol, Chia Piroti; Abstract data, Peyman Zafardoost; preparation of the manuscript, Peyman Zafardoost.

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