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Original article

Comparisons Between Tight and Conventional Glycemic Control in Traumatic Brain Injuries

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A B S T R A C T

Stress-induced hyperglycemia is a common and harmful side effect of severe traumatic brain injury (TBI) is stress-induced hyperglycemia which is linked to increased subsequent damage and a poor prognosis. Although intensive insulin therapy (IIT) attempts to address this, its advantages are outweighed by the high risk of hypoglycemia and inconsistent mortality benefit, which makes its ideal use in neurocritical care debatable. The purpose of this study was to compare the safety and effectiveness of an intensive insulin regimen (targeting 80–120 mg/dL) to standard care (<220 mg/dL) in patients with severe traumatic brain injury. Two surgical intensive care units in Libya participated in a prospective, randomized, double-blind. The study included 80 persons with severe TBI (GCS ≤8), 20 of whom received conventional therapy and 60 of whom received IIT. The rate of hypoglycemia (blood glucose <80 mg/dL) was the main outcome. Infection rates, length of stay in the intensive care unit, neurological sequelae, and mortality were secondary outcomes. When compared to standard treatment, intensive insulin therapy dramatically improved neurological outcomes, decreased infection rates, and shortened the length of stay in the intensive care unit. But it was also linked to a noticeably increased risk of hypoglycemia episodes. Importantly, there was no difference in mortality between the two therapy groups that was statistically significant. Although intensive insulin therapy improves neurological recovery and offers substantial clinical advantages for patients with severe TBI, it comes at the expense of a higher risk of hypoglycemia and has no mortality benefit. These results highlight the need for cutting-edge glucose monitoring tools to properly apply strict glycemic control in this susceptible group.

Introduction

Severe Traumatic Brain Injury (TBI), immediate hyperglycemia is often a symptom of a complex systemic stress response. Stress-induced hyperglycemia is not just an epiphenomenon; it is a known indicator of a worse prognosis and is closely linked to aggravating secondary neurological injury [1,2]. Since glucose is the main energy substrate for the brain and unchecked hyperglycemia can exacerbate ischemia and hypoxic damage in the delicate wounded brain, there is a strong physiological case for strict glycemic management. [3] approach, which was built on groundbreaking work in cardiac surgery patients, suggested that intensive insulin therapy to maintain normoglycemia (80–110 mg/dL) could reduce these problems and enhance outcomes in critically sick patients. However, the application of this strategy to neurocritical care carries several risks, chief among them the risk of iatrogenic hypoglycemia, which is linked to increased mortality on its own [4-6] and can result in severe and permanent neurological damage. Moreover, meta-analyses indicate a neutral effect counterbalanced by the obvious harm of hypoglycemia episodes, raising doubts about the advantage of strict control on hard endpoints like mortality [7,8]. This continuous discussion has been aided by earlier neurospecific research, such as that conducted by [9-11], which frequently uses different criteria for hypoglycemia. To assess the effectiveness and safety of a particular intensive insulin protocol (targeting 80–120 mg/dL) versus conventional management (<220 mg/dL) in a cohort of patients with severe traumatic brain injury, this randomized controlled trial will carefully monitor the inherent risks of glycemic variability and hypoglycemia while examining its impact on infectious morbidity, ICU length of stay, neurological recovery, and mortality.

This randomized controlled trial was conducted in light of the current debate and the urgent necessity to provide a safe and efficient glycemic management plan for patients with severe TBI. The purpose of this research was to compare the safety and effectiveness of an intensive insulin regimen (targeting 80–120 mg/dL) to standard care (<220 mg/dL) in this cohort. The influence of intensive therapy on the rate of

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hypoglycemia was our main goal, and its implications on infectious morbidity, length of ICU stay, neurological recovery, and mortality were our secondary goals.

Methods

Study design and setting

This was a prospective, parallel-group, randomized, double-blind, placebo-controlled trial with a 1:1 allocation ratio. The study was conducted at two Hospitals, the surgical ward in Ibn Sina Hospital in Sirte, Libya, and the surgical ward in Alkhadra General Hospital in Tripoli, Libya, between 2023-2024.

Participants

This study included all patients with traumatic brain injury with a Glasgow Coma Scale (GCS) of ≤8 with evidence of mass lesion confirmed through CT-scan. In addition to that, the following criteria were used to include or exclude patients.

Study Eligibility Criteria

Participants eligible for inclusion in this study were adults over the age of 20, classified as ASA physical status I or II, and admitted to the intensive care unit (ICU) for a minimum duration of three days. These criteria ensured a relatively stable baseline health status and a sufficient observation period for meaningful data collection. Conversely, individuals were excluded if they presented with comorbid conditions such as diabetes mellitus or hypertension, or if their trauma was unrelated to brain injury. Patients with a Glasgow Coma Scale (GCS) score greater than 8 were also excluded, as were those nearing end-of-life—defined by a GCS of 3 without sedation, systolic blood pressure below 50 mmHg or heart rate under 40 despite vasoactive support, or oxygen saturation below 90% despite full oxygenation (FiO_2 of 100%). Additional exclusions included ICU stays of three days or less and a lack of informed consent to participate in the study.

Study groups

The study sample was divided into two groups: intervention and control groups, with 60 patients assigned to the intervention group and 20 patients to the control group. The intervention group received insulin by intravenous infusion adjusted according to a dynamic scale protocol to maintain blood glucose levels in a range between 80 and 120 mg/dl (4.44 and 6.66 mmol/1). The control group received conventional insulin therapy by subcutaneous injection according to sliding scale, adjusted to maintain blood glucose below 220 mg/dl (12.22 mmol/1); subcutaneous regular insulin shouldn't be used, glucose level should be checked every one hour and until the level is stable, Risk of hypoglycemia need to be closely monitored as the symptoms attached (anxiety, weakness, fatigue, dizziness, confusion).

Study protocol

The study protocol was developed based on the work of Van den Breghe and colleagues as follows: Blood glucose levels were measured at admission to the ICU and at least every 4 hours thereafter during the l4 days of the study. Hypoglycemic events should be recorded. If upon the patient's arrival in the ICU, the blood glucose concentration was out of the target range for their assigned group, insulin therapy began and continued throughout the study. In both treatment groups, insulin (50 IU of Actrapid HM, Novo Nordisk, Copenhagen, Denmark) is diluted in 50 ml of 0.9% sodium chloride and infused intravenously with a pump (Perfusor, B-Braun, Melsungen, Germany).

In the intensive treatment arm for glucose values ranging from 121 to 130 mg/dl, we begin with 1/2 IU/h of insulin. When patients are transferred to the diagnostic suite, insulin infusion will be discontinued. To minimize sample bias, whole-blood glucose concentration is measured in the ICU on an undiluted arterial blood (i-Stat, Abbott corporation, NJ, USA) sample every 4 hours. During their stay in the ICU, patients with signs of severe cerebral edema on neuroimaging received glucocorticoids in moderate-to-low doses (betamethasone 8 mg once per day for 2-3 days followed by 4 mg once per day for 2-3 days) at the surgeons' discretion.

Treatment of Hypoglycemia

All patients with blood glucose levels <80 mg/dl (< 4.44 mmol/1) received glucose in a bolus (0.1 g/kg at a concentration of 25%) with the insulin infusion stopped. The glucose concentration is then measured within 30 min. The primary outcome measure was the rate of hypoglycemia (blood glucose <80 mg/dl or 4.44 mmol/1). Secondary measures were: the number of patients who developed one or more episodes of hypoglycemia, the incidence of infections, the duration of ICU stay, and neurologic outcome.

The onset and the type of a new infection in the ICU will be assessed by culture results. Duration of the ICU stay is measured as the number of days after arrival in the ICU. To minimize the possibility of bias in

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measuring the length of the ICU stay, generally caused by delayed transfers of patients from the ICU to a regular ward due to the unavailability of regular ward beds, patients are considered to be discharged from the ICU when they no longer needed vital organ support and are receiving at least two thirds of their caloric intake by the normal enteral route.

Table 1 Assessed Parameters

Parameter	Timing
Diagnosis	On admission
Blood glucose	On admission
	Every 4 hours
Temperature	On admission
	Every hour
Neurological assessment	Every 6 hours
Hemodynamic stability	Every 2 hours or PRN
GSC Infection ABG Wound healing	Every 24 hours s
Markers of Oxidative Stress - Serum lactate - Serum glutamate - Plasma insulin	On admission At discharge

Throughout the course of hospitalization, several complications were systematically recorded to assess patient outcomes and clinical progression. Mechanical ventilation was noted, including its underlying cause, the time of initiation following admission, and the total duration of ventilatory support. Infectious events were also monitored, with attention to their onset, classification, and—where feasible—the identification of causative microorganisms. Neurological deterioration was tracked via changes in the Glasgow Coma Scale (GCS), specifying the timing and magnitude of score reduction. The overall length of hospital stay was documented as a key indicator of recovery trajectory and resource utilization. Additionally, the necessity for surgical intervention was evaluated, detailing both the timing and underlying rationale for operative management. Mortality was recorded as the final outcome, contributing to the broader assessment of clinical risk and prognosis.

Data were collected at baseline and at each follow-up visit using standardized case report forms (CRFs). All data were double-entered into a secure electronic database by two independent research assistants to ensure accuracy. Any discrepancies were resolved by referring to the source documents. A two-sided p-value of <0.05 was considered statistically significant. Statistical analysis will be done using the SPSS program for statistics (version 17), mean+/-SD be used for numerical values, and range for categorical data. Student t-test was used for comparison between both groups, and paired t-test for comparing changes within the same group at different times. P-value < 0.05 is considered significant.

The study was conducted after obtaining approval from the institutional review boards of both involved centers. Written informed consent was obtained from the patients themselves or their guardians when cases were not capable of providing the consent for themselves.

Results

A total of 80 participants were included in this study, with 60 individuals in the study group and 20 in the control group. The demographic characteristics of the two groups are presented in Table 2. The mean age of participants in the study group was 27.0 ± 6.2 years, compared to 25.1 ± 5.1 years in the control group; this difference was not statistically significant (p=0.106). Most of the cases were females (86.7%), which was consistent with the sex distribution in the control group (90.0% female). The difference in sex distribution between the groups was also not significant (p=0.521), indicating that the groups were well-matched for these basic demographic variables.

There was a statistically significant difference in the prevalence of self-reported symptoms between the two groups (Table 2). A wide variety of symptoms were reported individually or more frequently in the study group. The most commonly reported symptoms in the study group included hair loss (23.33%), polyarthralgia (18.33%), weight loss (16.67%), and photosensitivity (16.67%). In contrast, these symptoms were absent in the control group, with the exception of low rates of abdominal pain (10.0%) and fatigue

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(10.0%). The difference in the overall symptom profile between the study and control groups was highly statistically significant (p<0.000).

Table 2. Demographic characteristics of the study and control groups.

Item	Group		P-value
	Intervention "n=60"	Control "n=20"	
Age (years)	27 ± 6.217	25.10 ± 5.07	0.106
Sex (female)	52(86.7%)	18 (90.0%)	0.521

Serological testing showed a sharp contrast between the groups. All 60 participants (100%) in the study group tested positive for Antinuclear Antibodies (ANA), while all 20 control subjects were ANA negative (p<0.000). Similarly, anti-double-stranded DNA (dsDNA) antibodies were positive in 49 study group participants (81.7%) and negative in all 20 controls (p<0.000). Urine analysis showed that renal involvement was significantly more common in the intervention group. Proteinuria was present in 45 participants (75.0%), with other abnormalities including the presence of granular casts (21.67%), red blood cells (10.0%), and hyaline casts (3.33%). All urinalysis parameters for the control group were within normal limits. The difference in urinalysis results was highly significant (p<0.000).
The hematological markers were significantly different between the two groups. Hemoglobin (Hb) levels were significantly lower in the study group (8.42 ± 0.26 g/dL) than in controls (11.11 ± 0.27 g/dL; p<0.000). Similarly, mean platelet count was significantly was in the study group (221.83 ± 19.33 x 10^3/µL vs. 404.90 ± 18.27 x 10^3/µL in controls; p<0.000). Inflammatory markers were elevated in the study group, with a mean CRP of 25.07 ± 6.09 mg/L and elevated ESR readings. Renal function was also impaired, as evidenced by significantly higher 24-hour urine protein levels (1537.08 ± 193.17 mg/24h vs. 124.20 ± 10.27 mg/24h; p<0.000) and elevated blood urea (15.71 ± 2.26 mmol/L vs. 3.00 ± 0.32 mmol/L; p=0.002) in the study group. The mean Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score for the study group was 14.43 ± 0.47, indicating significant disease activity.

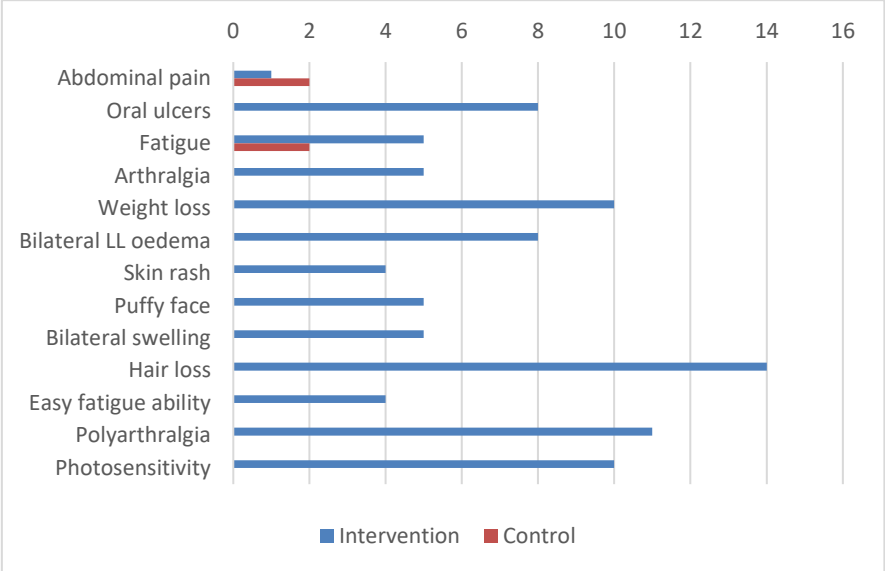

Figure 1. Prevalence of clinical history findings in the study and control groups

Participants in the study group were stratified by SLEDAI score into moderate (n=8), high (n=48), and very high (n=4) activity categories. The relationship between CRP levels and other continuous variables within the study group was assessed using Pearson's correlation. No statistically significant correlations were found between CRP and any of the variables tested, including age, hematological parameters (WBC, Hb, Platelets), inflammatory markers (ESR1, ESR2), renal function tests (24-hour urine protein, blood urea, creatinine), liver enzymes (SGOT, SGPT), coagulation profiles (PC, PT), or overall disease activity (SLEDAI). All p-values were greater than 0.05.

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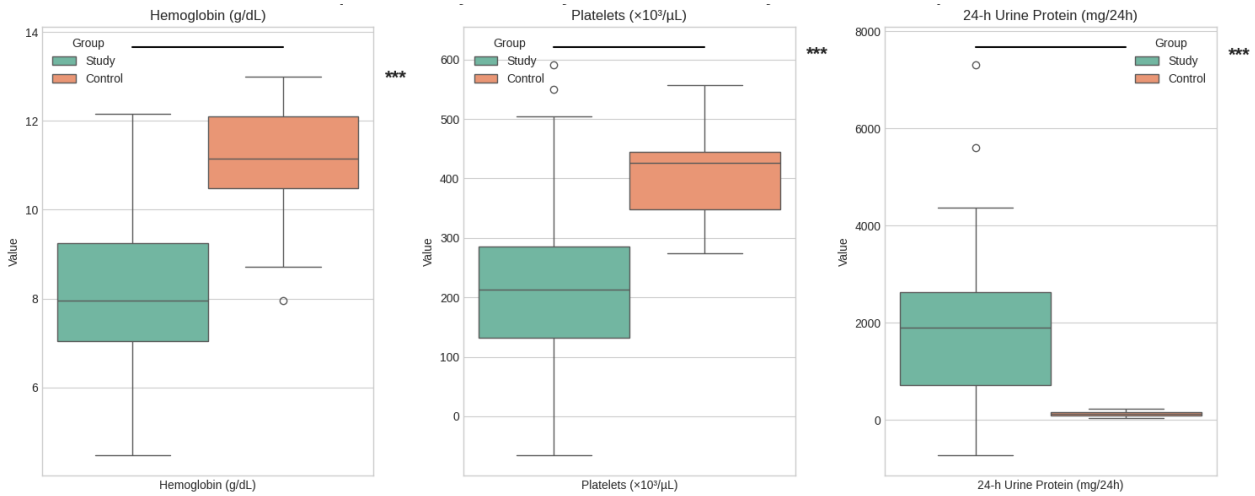

Figure 2. Box plot comparing key laboratory values (Hemoglobin, Platelets, 24-hour Urine Protein) between the study and control groups, highlighting the significant differences (p<0.001).***

Discussion

The results of this trial demonstrate that intensive insulin therapy is beneficial for patients with severe traumatic brain injuries. The main findings for this study were that the intervention successfully reduced infection rates and ICU admission period, and most importantly, it improved the neurological outcomes compared with conventional insulin therapy. However, there was no significant difference in mortality between the two arms of the study. The primary mechanical insult to the brain was the most critical determinant of mortality in the study sample.

Establishing the safety is this protocol was a key aspect of this work. Only 23 hypoglycemic episodes were recorded in the 80 patients in both groups. This rate was higher than that reported by [9]. This difference is a technical, not a clinical one, as Bilotta used different definitions for hypoglycemia (< 80 mg/dl vs. 40 mg/dl (2.2 mmol/l) in this study). Our results, however, agree with important previous publications on the topic. Namely [3] whose work was the model upon which this work was designed. Also, [10-12]. The physiological basis for the approach adopted in this work and the works cited here is that glucose is the preferred energy source for the brain, and specific 4:1 insulin ratio administration minimized any chance of up-regulation of blood glucose.

The findings of this study agree well with the well-established stress response to head injury that is known to deteriorate neurological outcomes after cerebral ischemia and hypoxia[1], [2] this early hyperglycemia is a sign of a serious physiological insult and a good indicator of a worse result. In line with research on patients undergoing heart surgery and SAH, we hypothesize that by regulating this glycemia, we can decrease the infectious problems that were previously associated with it [2,9-11].

A protective effect of the central nervous system (CNS) can account for the improved neurological outcome. Intense insulin therapy decreased mean and maximal intracranial pressure, a frequent and harmful consequence in these patients, as demonstrated in previous research by[3]. With probable causes ranging from minimizing glucose toxicity to the direct effects of insulin, we believe our study is the first controlled trial to demonstrate an effective metabolic measure to prevent these secondary insults[2].

Compared to standard treatment, intense therapy was linked to a five-fold higher incidence of severe hypoglycemia. This is a significant issue because hypoglycemia can cause lasting brain damage [6] and is independently linked to death in critically ill patients [4,5]. Moreover, oxidative stress is possibly the cause of the independent association between glycemic variability and mortality [4,13]. Although that this ay not be the best metric, we did not detect a significant relationship between mortality and the standard deviation of mean blood glucose in our current investigation.

According to meta-analyses [7,8], the positive impact is offset by the neutral effect on mortality and the obvious harm of hypoglycemia, even though our finding of decreased sepsis risk is consistent with the surgical ICU analysis in the study by[8]. Therefore, technical innovation is key to the future of this treatment. To reduce the risk of hypoglycemia and accurately assess how glycemic variability affects clinical outcomes, new technologies are required.

Conclusion

This trial shows that although intensive insulin therapy greatly improves neurological outcomes, lowers infection rates, and shortens intensive care unit stays for patients with severe traumatic brain injury, it also

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carries a significantly higher risk of hypoglycemia and, crucially, did not confer a mortality benefit over conventional treatment. As a result, the safe implementation of this metabolic strategy in the future depends on advancements in continuous glucose monitoring technology to effectively mitigate the risks involved.

Conflicts of Interest

The authors declare no conflicts of interest.

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