Intensive insulin therapy for preventing postoperative infection in patients with traumatic brain injury: A randomized controlled trial

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Abstract

Objective: To assess the effect of intensive insulin therapy (IIT) for preventing postoperative infection in patients with traumatic brain injury (TBI).

Methods: In total, 88 patients with TBI were randomly divided into 2 groups, 44 in each group. One group (group IIT) received IIT and the other group (group CIT) received conventional insulin therapy (CIT). This study was conducted between February 2013 and January 2016. Outcomes included infection rate, mortality, and neurological outcome (measured by the Glasgow Outcome Scale [GOS]).

Results: A total of 81 patients completed the study. IIT showed greater efficacy than CIT, with a decreased infection rate in the IIT group compared to the CIT group (31.9% vs 52.3%, \(P=0.03\)), and also a reduced duration of stay in intensive care unit (ICU) (IIT group, 4.5±2.1 days vs CIT group, 5.7±2.8 days, \(P=0.02\)). In addition, a significant difference in scores on the GOS scale was observed between the 2 groups (\(P=0.04\)). The mortality rates in hospital and at the 26-week follow-up were similar between the 2 groups.

Conclusion: IIT leads to a reduced infection rate, shorter stays in ICU, and improved neurological outcome.

Abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation, BGL = blood glucose level, CIT = conventional insulin therapy, GOS = Glasgow Outcome Scale, ICU = intensive care unit, IIT = intensive insulin therapy, TBI = traumatic brain injury.

Keywords: infection, intensive insulin therapy, randomized controlled trial, traumatic brain injury

1. Introduction

Hyperglycemia often occurs in patients with brain injury occasioned by cerebral trauma, ischemic stroke, and so on.\textsuperscript{[1-4]} Hyperglycemia has also long been associated with increased morbidity and mortality for such patients,\textsuperscript{[5-7]} and is associated with worse neurological outcomes after traumatic brain injury (TBI).\textsuperscript{[8,9]} In critically ill patients with TBI, hyperglycemia and insulin resistance are very common, even if those patients did not have diabetes previously.\textsuperscript{[10]}

It has been reported that intensive insulin therapy (IIT) aids in the normalization of blood glucose levels (BGLs) in patients with severe TBI,\textsuperscript{[10,11]} and can also significantly decrease the mortality and morbidity rates of such patients in the intensive care unit (ICU).\textsuperscript{[12,13]} A study conducted in the USA found that among patients under postoperative cardiac intensive care, those receiving IIT exhibited reduced morbidity (including infection rate) and reduced mortality compared to patients receiving conventional insulin therapy (CIT).\textsuperscript{[14]}

Since no existing randomized controlled trial has tested the effectiveness of IIT in preventing postoperative infection in patients with TBI, in this prospective randomized controlled trial, we compared IIT to CIT in patients with TBI in the ICU in China. We tested the hypothesis that IIT would reduce the infection rate and decrease the duration of ICU stay in patients with TBI.

2. Methods

2.1. Design

This study was designed as a randomized controlled trial. It was approved by the Medical Ethical Committee of Beijing Chaoyang Hospital and was conducted at Beijing Chaoyang Hospital from February 2013 to January 2016. Eighty-eight patients with TBI were recruited and randomly assigned to an IIT group and a conventional insulin therapy (CIT) group, with a 1:1 allocation ratio. All patients met the inclusion/exclusion criteria. Written informed consent was obtained from each patient’s closest family member. TBI severity was assessed by the Acute Physiology and Chronic Health
Evaluation (APACHE II)\textsuperscript{[15]} with higher values indicating more severe illness\textsuperscript{[15]}

2.2. Inclusion and exclusion criteria

The inclusion criteria included age $\geq$18 years, a Glasgow Coma Scale score $< 8$, and admission to the postoperative neurosurgical ICU. Patients were excluded in case of terminal disease, cachexia, shock lasting 12 hours or more, death in the first 48 hours, pregnancy, or if they declined to participate.

2.3. Randomization and blinding

Randomization was achieved by the stratified block randomization method with a computerized number generator using Software SAS (version 8.1; SAS Institute, Inc., Cary, NC). After randomization, group allocation of patients was concealed in opaque, sequentially numbered, and sealed envelopes. The patients, the outcome assessor, and the data analyst were blinded to the treatment allocation.

2.4. Participants and recruitment

All participants were recruited through the clinic of the Department of Neurosurgery at Beijing ChaoYang Hospital. All subjects were randomized to either the IIT or CIT group only after the clinical evaluation and ultrasound scan. All investigators were trained in administration of the treatments before the study. Eligible patients and their closest family members were informed about the research and given an information sheet. All consenting patients were then administered either IIT or CIT.

2.5. Intervention

2.5.1. Nutrition schedule. During the first 24 hours, all patients were given an intravenous infusion of 0.9% sodium chloride solution at a rate of 1 mL/kg/h. Then the standardized schedule of parenteral and/or enteral nutrition was initiated. This schedule continued until each patient was discharged from the ICU or on postoperative day 14. In addition, all patients received standard glycemia care at the end of the study to maintain their BGL below 200 mg/dL (11.10 mmol/L).

2.5.2. Cerebral edema therapy. During the stay in ICU, all patients with signs of severe cerebral edema on neuroimaging scans were given betamethasone, 8 mg/day for 2 to 3 days at first, followed by 4 mg/day for an additional 2 to 3 days at the surgeons’ discretion.

2.5.3. IIT intervention. In the IIT group, an insulin infusion was started if the BGL rose above 6.11 mmol/L, and was then adjusted so as to maintain BGL in a range of 4.4 to 6.11 mmol/L, as recommended by previous studies\textsuperscript{[11,13]} The continuous dose of insulin was set at 50 IU/h for both groups\textsuperscript{[11,13]} The conventional approach was adopted after patients were discharged from ICU. The insulin dose was adjusted based on the measurements of whole-blood glucose in undiluted arterial blood, which was measured every 4 hours.

2.5.4. CIT intervention. In the CIT group, insulin (50 IU in 50 mL of 0.9% saline) was infused using a pump (Perfusor-FM, B. Braun, Melsungen, Germany). It was initiated if BGL rose above 11.94 mmol/L. CIT was adjusted so as to maintain BGL at 10 to 11.11 mmol/L. When BGL sank below 10 mmol/L, the insulin infusion was stopped.

2.6. Outcome measures

The primary outcomes were infection rate and neurological outcome. Infections included pneumonia, sepsis, and urinary and wound infections, and were defined according to the National Nosocomial Infection Surveillance System\textsuperscript{[16]} Two assessors independently evaluated the date of onset and the type of infection for any infective disease observed. Neurological outcome was measured by the Glasgow Outcome Scale (GOS).

The secondary outcomes included duration of ICU stay and mortality rate. Neurological outcome and mortality rate were evaluated at 6 months follow-up. If the patient could not be contacted within 10 days of the initial attempt, they were considered to be lost to follow-up.

2.7. Statistical analysis

The required sample size for this study was estimated to be 38 patients in each group, based on a hypothesized effect size of a 20% difference between the 2 groups, $\alpha = 0.05$ (2-sided) and $\beta = 0.20$. Assuming an infection rate of 46%\textsuperscript{[17]} and a 15% dropout rate, at least 88 patients (with 44 in each group) needed to be recruited to this study. All outcome data were analyzed on an intention to treat basis. Chi-square tests and $t$ tests were used to analyze the categorical and the continuous data, respectively, with relative risks and 95% confidence intervals. A $P$ value $< 0.05$ was taken to indicate a significant statistical difference.

3. Results

A total of 147 patients with TBI were initially assessed for entry into the study (Fig. 1). Of them, 59 patients were excluded because of failure to meet inclusion and exclusion criteria ($n = 51$), or refusal to enroll in the study ($n = 8$). In the end, 88 patients were included and randomly assigned to the IIT or CIT groups, with 44 patients in each group. All 88 patients completed the treatment, however 7 patients were lost to follow-up (Fig. 1).

The characteristics of the patients in both groups at baseline are shown in Table 1. The 2 groups did not differ significantly in terms of age, sex, race, medical history, body mass index, Glasgow Coma Scale, APACHE II score, or BGLs as investigated at baseline (Table 1).

The infection rate was 31.9% (13/44) in the IIT group, which was significantly lower than the 52.3% (23/44) infection rate in the CIT group ($P < 0.05$, Table 2). The GOS scale at 6 months showed a between-groups difference with 59.1% (26/44) of patients scoring between 1 and 3 and 40.9% (18/44) scoring 4 or 5 in the IIT group, compared to 79.5% (35/44) and 20.5% (9/44) respectively in the CIT group ($P = 0.04$, Table 2). The duration of ICU stay was 4.5 ($\pm$ 2.1) days in the IIT group, compared to 5.7 ($\pm$ 2.8) days in the CIT group ($P = 0.02$, Table 2). No significant differences were found between the 2 groups in terms of mortality, both in hospital and at follow-up ($P > 0.05$, Table 2).

4. Discussion

Previous studies have reported the use of IIT in the treatment of patients with TBI\textsuperscript{[18–20]} One study found no effect of IIT on neurological outcome, duration of ICU stay, or sepsis rates, in patients with TBI\textsuperscript{[20]} Another study reported that IIT significantly increased the risk of hypoglycemic episodes and shortened ICU stays ($P < 0.05$), but had no effect on infection rates, GOS scores, or mortality at months.$^{[18]}$ A further study of IIT for
patients with TBI investigated infection rates, days spent in ICU, in-hospital mortality, and long-term neurological outcome.\textsuperscript{19} The key finding of this study was that IIT cannot only decrease infection rate and days spent in the ICU, but it can also improve neurological outcome at the 6-month follow-up.\textsuperscript{19} This finding is consistent with the present study in showing that IIT can reduce infection rate and days in ICU, and also improve neurological outcome in patients with TBI.\textsuperscript{19}

In this study, the patients with TBI in the IIT group showed a significantly lower infection rate ($P = 0.03$), shorter stays in ICU ($P = 0.04$), and an improvement in neurological outcome ($P = 0.02$), compared to patients in the CIT group, suggesting that IIT had a positive effect on the infection rate and duration of ICU stay, and also improved the neurological outcome. On the other hand, this study demonstrated that IIT did not reduce the mortality rate of patients with TBI, neither in hospital nor at the 6-month follow-up.

This study has several limitations. First, the most important limitation is the lacking blind for insulin intervention in this study. In addition, this study was based at a single-center, and was only conducted at Beijing ChaoYang Hospital of Capital Medical University, which may restrict the generalization of our findings. Third, some differences in clinical severity between the 2 groups may have affected the primary and secondary outcomes, such as duration of ICU stay and infection rate, even though no differences in APACHE II score were found at baseline. Finally,

### Table 1

| Variable                        | IIT group (n=44) | CIT group (n=44) | P    |
|---------------------------------|------------------|------------------|------|
| Age, years                      | 46.7 (10.4)      | 45.1 (10.7)      | 0.48 |
| Sex                             |                  |                  |      |
| Male                            | 30 (68.2)        | 28 (63.6)        | 0.65 |
| Female                          | 14 (31.8)        | 16 (36.4)        | 0.65 |
| Race                            |                  |                  |      |
| Uyghur ethnicity                | 3 (6.8)          | 5 (11.4)         | 0.73 |
| Han ethnicity                   | 41 (93.2)        | 39 (88.6)        | 0.73 |
| Medical history                 |                  |                  |      |
| Diabetes                        | 8 (18.2)         | 9 (20.5)         | 0.79 |
| Hypertension                    | 13 (29.5)        | 14 (31.8)        | 0.82 |
| Smoking                         | 12 (27.3)        | 10 (22.7)        | 0.62 |
| Body mass index, kg/m$^2$       | 26.3 (5.0)       | 27.9 (4.9)       | 0.70 |
| Glasgow Coma Scale              | 5.4 (2.3)        | 5.3 (2.3)        | 0.84 |
| APACHE II score                 | 28.6 (11.7)      | 28.3 (10.9)      | 0.90 |
| Admission blood glucose, mg/dL  | 182.6 (33.7)     | 179.8 (31.9)     | 0.69 |

Data are present as mean ± standard deviation or number (%). APACHE II= Acute Physiology and Chronic Health Evaluation; CIT = conventional insulin therapy; IIT = intensive insulin therapy.

### Table 2

| Variable                        | IIT group (n=44) | CIT group (n=44) | P    |
|---------------------------------|------------------|------------------|------|
| Infections                      |                  |                  |      |
| Pneumonia                       | 13 (31.9)        | 23 (52.3)        | 0.03 |
| Urinary infections              | 3 (6.8)          | 6 (13.6)         | 0.65 |
| Wound infections                | 2 (4.5)          | 3 (6.8)          | 0.65 |
| Sepsis                          | 1 (2.3)          | 1 (2.3)          | 0.65 |
| Pneumonia and urinary infections| 1 (2.3)          | 3 (6.8)          | 0.65 |
| Urinary and wound infections    | 1 (2.3)          | 2 (4.5)          | 0.65 |
| Pneumonia and sepsis            | 1 (2.3)          | 1 (2.3)          | 0.65 |
| Pneumonia and wound infections  | 1 (2.3)          | 1 (2.3)          | 0.65 |
| Urinary infections and sepsis   | 0 (0.0)          | 1 (2.3)          | 0.65 |

GOS scale at 6 months

| GOS scale at 6 months | IIT group (n=44) | CIT group (n=44) | P    |
|-----------------------|------------------|------------------|------|
| 1, 2, 3               | 26 (59.1)        | 35 (79.5)        | 0.04 |
| 4, 5                  | 18 (40.9)        | 9 (20.5)         | 0.04 |

Duration of ICU stay, days

| Duration of ICU stay, days | IIT group (n=44) | CIT group (n=44) | P    |
|---------------------------|------------------|------------------|------|
| 45 (2.1)                  | 5.7 (2.8)        | 0.02             |

Mortality

| Mortality | IIT group (n=44) | CIT group (n=44) | P    |
|-----------|------------------|------------------|------|
| 22 (50.0) | 23 (52.3)        | 0.83             |

In-hospital

| In-hospital | IIT group (n=44) | CIT group (n=44) | P    |
|-------------|------------------|------------------|------|
| 12 (27.3)   | 14 (31.8)        | 0.64             |

Follow-up at 6 months

| Follow-up at 6 months | IIT group (n=44) | CIT group (n=44) | P    |
|-----------------------|------------------|------------------|------|
| 10 (22.7)             | 9 (20.5)         | 0.80             |

Data are present as mean ± standard deviation or number (%). CIT = conventional insulin therapy, GOS = Glasgow Outcome Scale, ICU = intensive care unit, IIT = intensive insulin therapy.
factors relating to the ICU setting in this study, such as the use of sedation and mechanical ventilation may represent a further limitation because such factors might have masked the clinical signs and symptoms of hypoglycemia in patients with TBI.

This study showed that IIT for patients with TBI not only decreased infection rates and the duration of ICU stay, but also enhanced neurological outcome. Further studies with larger sample sizes are needed to verify this result.

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