Intensive Insulin Therapy Versus Conventional Glucose Control In Traumatic Brain Injury Patients Who Are On Parenteral Nutrition

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ABSTRACT

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Parenteral nutrition (PN) is a valuable life saving intervention, which can improve the nutritional status of hospitalized malnourished patients. PN is associated with complications including hyperglycemia. This study was conducted to compare two methods of blood glucose control in traumatic brain injury patients who are on PN.

Materials & Methods: This study is a randomized, open-label, controlled clinical trial with blinded end assessment. This study was done in the surgical intensive care unit of Beni-Suef University hospital after obtaining approval from the ethical committee of the Institution and obtaining consent from relatives of the patients involved in the study. Seventy critically ill patients were chosen randomly according to the inclusion criteria from cases admitted to Beni-suef university hospital, then divided into two groups randomly:

Group I (Intensive insulin therapy): 35 patients received continuous insulin infusion to maintain glucose levels between 4.4mmol/l (80 mg/dl) and 6.6mmol/l (110 mg/dl).

Group II (Conventional therapy): 35 patients not received insulin unless glucose levels greater than 10 mmol/l (>180 mg/dl).

Results: In our study, it was shown that mean glucose concentration were significantly lower in IIT group vs conventional group. No hypoglycemic episode occurred in two groups. Triglyceride and C-reactive protein was decreased in the IIT group, significantly. There were also significant differences in the electrolytes, with magnesium and phosphorus being lower in the IIT group.

Conclusion: In this study, Intensive insulin group improved some of parenteral such as hyperglycemia, hypertriglyceridemia and electrolyte imbalances compared to Conventional insulin group.

Keywords: Glycemic Control, Intensive Insulin Therapy, Parenteral Nutrition

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I. INTRODUCTION

Parenteral nutrition (PN) is a form of intravenous nutritional support, which can improve the nutritional status of hospitalized malnourished patients. PN may cause metabolic changes such as hyperglycemia, hypertriglyceridemia, electrolyte imbalances and steatosis(1).

Energy requirements were estimated as 25 Kcal/Kg ideal body weight as proposed by European Society for Clinical Nutrition and Metabolism (ESPEN) guideline. The requirements of macro- and micro-nutrients were also calculated based on ESPEN guideline and this was used to estimate the composition of PN for each individual patient. Dextrose (dextrose 10%) was infused for 8-10 hours, lipid emulsion (intralipid 10%) for 6 hours and amino acids emulsion (amino acid 10%) for 4 hours. Vitamins and minerals were injected through normal saline solution. Fluid load was assessed (by recording the fluid output minus input) and controlled for each patient (2).

Hyperglycemia induced by parenteral nutrition has been shown to exacerbate secondary brain injury and independently predict poor neurologic outcomes in patients with severe traumatic brain (3).

Stress-induced hyperglycemia occurs frequently in critically ill patients and has been associated with increased morbidity and mortality in both diabetic and non-diabetic patients and in patients with traumatic injury, stroke, anoxic brain injury (4).

The mechanisms by which hyperglycemia affects outcomes could be related to suppressive effects on immune function and an associated increased risk of infection, endothelial damage, hepatocyte

mitochondrial damage, and potentiation of tissue ischemia due to acidosis or inflammation (5).

A previous comparison of critically ill-patients randomly assigned to either intensive insulin therapy (IIT) or conventional glucose treatment (CGC) showed that the first group whose blood glucose (BG) was maintained at 4.4-6.6mmol/l had significantly lower morbidity and mortality rates (6). The results of other studies, however, have been inconsistent since they resulted in reductions in morbidity but not mortality, increased mortality, due to a higher incidence of hypoglycemia in patients on tight glycemic control (7).

The risk of mortality and the consequences of hypoglycemia in critically ill-patients under IIT and especially in patients with brain trauma, are a serious concern, since hypoglycemia is associated with worsening in the Glasgow Coma Scale score (GCS) (8).

II. METHODS AND MATERIAL

Type of the study

This study is a randomized, open-label, controlled clinical trial with blinded end assessment. This study was done in the surgical intensive care unit of Beni-Suef University hospital after obtaining approval from the ethical committee of the Institution and obtaining consent from relatives of the patients involved in the study.

Sample size

Seventy critically ill patients were chosen randomly according to the inclusion criteria from cases admitted to Beni-suef university hospital, then divided into two groups randomly:

Group 1 (Intensive insulin therapy): 35 patients received continuous insulin infusion to maintain

glucose levels between 4.4mmol/l (80 mg/dl) and 6.6mmol/l (120 mg/dl).

Group II (Conventional therapy): 35 patients not received insulin unless glucose levels greater than 10 mmol/l (>180 mg/dl).

All chosen patients were subjected to the following: On arrival in the ICU after history taking from relatives, full monitoring to patients and full assessment for (patients intubation, ventilator parameters, O₂ saturation, End tidal CO₂, blood pressure, heart rate and respiratory rate). Patients were divided into two groups:

Group I (Intensive treatment group):

Patients in the intensive treatment group received continuous intravenous insulin infusion (50 IU of regular insulin in 50 ml of 0.9 percent sodium chloride) according to insulin infusion protocol (9). If BG >150 mg/dl we gave initial bolus by dividing initial BG by 70 and round to nearest 0.5 U. After bolus we start infusion at same hourly rate as bolus. If BG <150 mg/dl we divided initial BG by 70 for initial hourly rate with no bolus. In this group, Blood glucose level was maintained between 4.4mmol/l (80 mg/dl) and 6.6mmol/l (120 mg/dl). We discontinued the infusion when glucose level was equal or less than 4.2mmol/l (75 mg/dl) and initiated dextrose 10% infusion 0.5g/kg/h. If glucose levels decreased to less than 3.3mmol/l (60 mg/dl), we decided to treat hypoglycemia according to a standardized hypoglycemia protocol. Blood glucose was checked every 1 hour in this group.

Group II (Conventional treatment group):

Patients in this group not received insulin during ICU stay unless their glucose exceeds 10mmol/l (>180 mg/dl). If blood glucose concentration between 11.1 (200 mg/dl) and 13.9mmol/L (250 mg/dl), patients received an intravenous bolus of 4 units insulin every

hour until the glucose concentration less than 11.1 mmol/L (<200 mg/dl). In this group, BG was measured every 1 hour.

Parenteral nutrition

The patients' energy requirements were estimated as 25 kcal/kg ideal body weight as proposed by the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines. The requirements of macro- and micro-nutrients were also calculated based on ESPEN guidelines and this was used to estimate the composition of PN for each individual patient. Glucose (glucose 25%) was infused for 8-10 hours through central vein, lipid emulsion (Intralipid 10%) for 6 hours and amino acids emulsion (amino acid 10%) for 4 hours. Vitamins and minerals were injected through normal saline solution. Fluid load was assessed (by recording the fluid output minus input) and controlled for each patient.

Measurements (Assessment)

-BG concentration was measured every 1 hour by glucometer and we confirmed it by venous sample every 24 hours and The following parameters were measured and recorded at 7th and 14th day for each patient:

- Mid- arm circumference
- Liver functions test (ALT, AST)
- Lipid profile (HDL, LDL, Triglyceride)
- Blood electrolyte (sodium, potassium, Mg, Ph)
- C reactive protein

III. RESULTS AND DISCUSSION

This study included 70 patients with ages ranging 18-60 years. There were no differences between the two study groups in demographic variables of age and Glasgow coma scale.

Table (1): Demographic Data of Intensive insulin group and Conventional insulin group

	Intensive insulin therapy (n=35)	Conventional insulin therapy (n=35)	P value
Age (Year)			
Range	21-56	21-54	0.728
Mean±SD	37.1±9.9	37.9±9.9	
Glasgow coma scale(GCS)			
Range	6-9	6-9	0.914
Mean±SD	7.4±1.1	7.5±1.1	

SD: Standard deviation

*: P-value < 0.05 (Significant)

Figure(1) Descriptive statistical analysis of blood glucose venous sample per day and showed that mean blood glucose concentration were statistically significant from 4th to 14th day that was lower in IIT group vs conventional group and its respective graphical presentation was shown in figure(1):

Figure (1)

Figure (2): Descriptive statistical analysis of mid arm circumference and showed There was an insignificant increase in mid arm circumference and its respective graphical presentation was shown in figure (2):

Figure(2)

Figure(3): Descriptive statistical analysis of lipid profile (HDL) showed statistically significant difference between two groups that HDL increase in IIT group in 14th day compared to conventional insulin group and its respective graphical presentation was shown in figure (3):

Figure(3)

Figure(4): Descriptive statistical analysis of lipid profile (LDL) showed statistically significant difference between two groups as that LDL increase in IIT group in 14th day compared to conventional insulin group

and its respective graphical presentation was shown in figure (4):

Figure(4)

Figure(5):Descriptive statistical analysis of lipid profile (TG) showed statistically significant difference between two groups as (TG) decreased in IIT group in 14th day and its respective graphical presentation was shown in figure (5):

Figure(5)

Figure(6):Descriptive statistical analysis of Magnesium showed statistically significant difference between two groups as (Mg) decreased in IIT group in 7th and 14th days and its respective graphical presentation was shown in figure (6):

Figure(6)

Figure(7):Descriptive statistical analysis of Phosphorous showed statistically significant difference between two groups as (ph) decreased in IIT group in 7th and 14th days and its respective graphical presentation was shown in figure (7):

Figure(7)

Figure(8):Descriptive statistical analysis of C reactive protein showed statistically significant difference between two groups as (C reactive protein) decreased in IIT group in 7th and 14th days and its respective graphical presentation was shown in figure (8):

Figure(8)

Discussion

Parenteral nutrition (PN) is a form of intravenous nutritional support, originally developed at the Pennsylvania University of Medical School in 1968 to support malnourished surgical patients ⁽⁹⁾. PN may cause metabolic changes such as hyperglycemia, hypertriglyceridemia, electrolyte imbalances and steatosis. Hyperglycemia has been shown to exacerbate secondary brain injury and independently predict poor neurologic outcomes in patients with severe traumatic brain injury ⁽¹⁾.

A previous comparison of 1548 critically ill-patients randomly assigned to either intensive insulin therapy (IIT) or conventional glucose treatment (CGC) showed that the first group whose blood glucose (BG) was maintained at 4.4-6.1 mmol/l had significantly lower morbidity and mortality rates. The results of other studies, however, have been inconsistent since they resulted in reductions in morbidity but not mortality, increased mortality, due to a higher incidence of hypoglycemia in patients on tight glycemic control⁽⁶⁾. In the largest randomized control trial conducted, which included 6104 patients, the IIT group not only had more severe hypoglycemia but also had increased mortality with no benefits in terms

of intensive care unit (ICU) stay or infection rates⁽⁷⁾. The risk of mortality and the consequences of hypoglycemia in critically ill-patients under IIT and especially in patients with brain trauma, are a serious concern, since hypoglycemia is associated with worsening in the Glasgow Coma Scale score (GCS)⁽⁸⁾.

Due to the fact that previous studies were inconsistent and did not assess PN complications or traumatic brain injury-ICU patients, the present study was designed to compare hypo/hyperglycemic episodes and PN complications in IIT and CGC in traumatic brain injury ICU patients who received PN. It was hypothesized that an IIT would result in fewer hyperglycemic episodes in these patients without any hypoglycemia and improvements in outcome assessments using mid-arm circumference, liver function tests, lipid profiles(HDL,LDL and Triglycerides) and inflammatory status.

In our study, it was shown that mean glucose concentration were significantly lower in IIT group vs conventional group. No hypoglycemic episode occurred in two groups. Triglyceride and C-reactive protein was decreased in the IIT group, significantly. There were also significant differences in the electrolytes, with magnesium and phosphorus being lower in the IIT group.

Van den Berge et al.⁽⁷⁾ report results from a meta-analysis of 26 studies involving over 13,500 patients. compared IIT versus conventional treatment among surgical intensive care patients, predominantly PN fed. Fasting BG targets were 4.4-6.1 mmol/L and 10-11.1 mmol/L in the intensive and conventional groups, respectively. They demonstrated a 34% decrease in mortality with IIT. Nevertheless, patients who underwent IIT had lower levels of intracranial pressure, less seizures, and a better prognosis after 6 and 12 months following hospital discharge

In another randomized controlled trial of 97 patients with severe traumatic brain injury (STBI), *Bilotta et al.* compared routine management of BG and insulin injection if BG was more than 12.2 mmol/l versus IIT to maintain BG at 4.4-6.7 mmol/l, a significantly reduction in ICU stay was observed in IIT group⁽¹⁰⁾.

Only *Cheung et al.*⁽¹¹⁾ clearly outlined treatment of hyperglycemia in their patients. Their protocol called for an insulin infusion for all patients irrespective of their inpatient location if during PN treatment blood sugars were persistently above 10 mmol/L. Treatment of hyperglycemia with insulin infusion was associated with an increased rate of complications, although not statistically significant for death. There were no documented cases of hypoglycemia in patients receiving insulin infusions. Incidentally, the mean blood glucose levels for these patients were significantly higher than patients who did not require insulin therapy, suggesting that insulin infusions were inadequately administered. This was the only study in our review to examine treatment of hyperglycemia, and the evidence is inconclusive regarding harm or benefit of the use of insulin infusions in patients receiving PN, furthering the need for more evidence regarding treatment of hyperglycemia in PN patients

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our review to examine treatment of hyperglycemia, and the evidence is inconclusive regarding harm or benefit of the use of insulin infusions in patients receiving PN, furthering the need for more evidence regarding treatment of hyperglycemia in PN patients

Pasquel et al.⁽¹²⁾ conducted a retrospective study of 276 hospitalized patients, in the ward and the intensive care unit at the Grady Memorial Hospital, Atlanta, Georgia, United States during the year 2006. Blood glucose levels on admission, pre-PN, within 24 hours of initiation of PN, and during days 2–10 of PN were included in the analysis. Hyperglycemia was defined as a blood glucose level above 6.7 mmol/L. The monitoring and treatment of these patients was not outlined in the methodology. Outcome measures included mortality, development of any infections, length of stay (LOS), and renal failure. The mean duration of PN was 15 ± 24 days. The mean daily blood glucose on admission was 7.7 ± 4.7 mmol/L. The mean blood glucose prior to initiation of PN was 6.8 ± 1.8 mmol/L and increased to a mean blood glucose of 8.1 ± 2.4 mmol/L within 24 hours and remained elevated at 7.8 ± 2.2 mmol/L for the remainder of the days analyzed.

Sarkisian et al.⁽¹³⁾ conducted a retrospective study of 100 hospitalized patients in the Foothills Medical Centre, Calgary, Canada. This cohort excluded critically ill individuals unlike the preceding three studies outlined.⁽¹⁴⁾ Mean blood glucose values were calculated for each patient based on the total number of readings during their first 9 days receiving PN including serum and finger prick readings. Hyperglycemia was defined as mean blood glucose levels above 10 mmol/L. Outcomes measured included development of any infection, acute coronary event, acute renal failure, LOS, ventilator use, ICU admission, and death. Additionally, this group reviewed the median frequency of glucose monitoring in both euglycemic and hyperglycemic patients and

the association of the frequency of monitoring with mortality. This study showed significantly increased mortality in patients with mean blood sugars greater than 10 mmol/L while receiving PN after adjusting for age, gender, and previous diabetes status, when compared to a lower blood glucose group. **Sarkisian et al.**⁽¹³⁾ did not find an association between hyperglycemia and acute coronary events, renal failure, infection, hospital length of stay, ventilator use, or admission to a critical care unit. This may be in part due to the less critically ill population studied in comparison to the other studies which included both critically ill and noncritically ill patients.

Liop J et al.⁽¹⁵⁾ showing that hypertriglyceridemia was associated with a high BG concentration. In this context, hyperglycemia could be a marker of disease severity and this severity was improved with IIT.

Green DM et al ⁽¹⁶⁾. showing that there was an insignificant increase in mid-arm circumference in the IIT group. This may be due to insulin's anabolic function and its role in fat and protein synthesis. In our study there was significant increase in mid-arm circumference in the IIT group.

Jeschke MG et al ⁽¹⁷⁾. showing that intensive insulin therapy leads to a reduction in C-reactive protein in the IIT group although this marker increased in the CGC group, possibly due to hyperglycemia. Liver function tests were not different between the two groups. In our study there was significant decrease in C-reactive protein in the IIT group.

Wiener RS et al ⁽¹⁸⁾. showing that intensive glucose control did not significantly alter mortality among critically ill patients. In keeping with the trials included in the meta-analysis, patients in the trial who were assigned to intensive glucose control, as compared with those assigned to conventional control,

had lower blood glucose levels, received more insulin, and had more episodes of severe hypoglycemia.

Langouche L et al ⁽¹⁹⁾. showing that the TG concentration of the IIT group was significantly lower than that of the CGC group. This may be due to the insulin infusion, which leads to an increase in lipoprotein lipase activity that the destruction in triglyceride enriched particles and an increase in HDL. It should be noted that HDL and TG are negatively correlated. In our study there was significant decrease in TG concentration in the IIT group.

It is clear from our data that lowering glucose concentrations to near normal levels by intravenous insulin infusion did not lead to PN complications such as hyperglycemia, hypertriglyceridemia and electrolyte imbalances and hypoglycemic episodes were not observed in the IIT group because Blood glucose was checked every 1 hour in this group. But complications of PN reduced. In contrast to previous studies that showed that hyperglycemia induced by PN strongly predicted adverse PN outcomes.

IV. CONCLUSION

In this study, Intensive insulin group improved some of parenteral such as hyperglycemia, hypertriglyceridemia and electrolyte imbalances compared to Conventional insulin group.

V. LIMITATION

This study is limited in that it has a small sample and thus further data collection is warranted before concluding on any of the outcome measures including patient survival or mortality.

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