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Intensive insulin therapy reduces infections in patients on parenteral nutrition- A randomized clinical trial

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Abstract

Introduction: Hyperglycemia is a common problem encountered in hospitalized patients, especially in critically ill patients due to stress and using parenteral nutrition. Uncontrolled hyperglycemia may be associated with increased infection risk. The principal benefit of intensive insulin therapy is a decrease in infection-related complications and mortality. The aim of this study was the assessment of IIT effect on pathogen growth in ICU patients. **Materials and Methods:** We conducted a randomized controlled trial study where patients with brain trauma in grade 2 and 3 that received at least 50% of nutritional needs from parenteral nutrition. They randomly assigned to receive IIT or conventional glucose control. Pathogen growth, mortality, survival, APACHE II score, duration of hospital stay was assessed.**Results:** Of 29 patients randomized, 26 patients completed the study. Survival duration, ventilator dependency and pathogen growth was improved in tight control group but not significant between two groups due to low sample size.**Conclusion**: In our study, IIT reduced pathogen growth without hypoglycemic episodes in head trauma patients.**[GMJ. 2012;1(1):2-7]**

Keywords: Pathogen growth - parenteral nutrition - intensive insulin therapy - hypoglycemia

Introduction

Parenteral nutrition (PN) is a form of intravenous nutritional support, originally developed at the University of Pennsylvania School of Medicine in 1968 to support malnourished surgical patients (1).It has been well established that PN has a beneficial effect in improving the nutritional status of hospitalized malnourished patients(2).PN is predominately used in those patients who are unable to receive nutrition either orally or enterally largely due to intestinal failure. Despite the life saving benefits attributed to PN, it is known to be associated with a number of short- and longterm complications including

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liver disease, catheter-related sepsis, septic shock, fluid and electrolyte abnormalities, and hyperglycemia.

Significant alterations to glucose metabolism occur under conditions of stress such as trauma, burn, major surgery, and sepsis. Stress-induced hyperglycemia is the result of increased sympathomimetic activity and increased release of counterregulatory hormones and pro-inflammatory cytokines. Counterregulatory hormones enhance glycogenolysis and gluconeogenesis to increase glucose production(3).For instance, epinephrine enhances glycogenolysis in the liver and skeletal muscles and increases gluconeogenesis in the kidneys. Growth hormone inhibits peripheral glucose uptake and stimulates gluconeogenesis. Proinflammatory cytokines are inflammatory mediators that also contribute to increasing glucose production by stimulating gluconeogenesis and glycogenolysis and by indirectly increasing the release of counterregulatory hormones such as glucagon and cortisol (4). Furthermore, proinflammatory cytokines contribute to insulin resistance by inhibiting insulin release. The end result of these physiologic changes is increased endogenous glucose production coupled with insulin resistance that leads to stress-induced hyperglycemia. Hypermetabolism in the patients under stress due to trauma or infection is associated with the increased muscular proteolysis, urea production in the liver, negative nitrogen balance, increased glucose production and fat mobilization (5). The mechanism of harm from hyperglycemia on various organ systems has not been well defined but it is known that hyperglycemia alters the activity of phagocytes, interfering with neutrophil and monocyte functions (6). Hyperglycemia also increases inflammatory cytokines, oxidative stress andpromotes apoptosis (4). Hyperglycemia may playan important role in altering leukocyte function, includingthe function of polymorphonuclear neutrophils (PMNs) (7). Cell and tissue injury caused by hyperglycemia through oxidative stress adversely affects the immune, cardiovascular and nervous system as well ashemostasis, inflammation, and endothelial cell function (8).

Three recent studies of hospitalized patients including both critically ill and noncritically ill, identified PN associated hyperglycemia as a risk factor for development of infection, cardiac, and renal dysfunction and increased mortality (9). The purpose of this studywas to compare the effects of two methods of glucose control in patients on parenteral nutrition on pathogen growth.

Material and methods

Subjects

This study was a randomized controlled trial of patients with traumatic brain injury that didn't need surgery and was carried out in January – June 2011 in ShahidKamyab hospital Of Mashhad , Iran .Patients aged 18 years or older with GCS 4-9 that had indications of parenteral nutrition, were eligible for the study. Patients received at least 50% of calorie from parenteral nutrition. Exclusion criteria were liver failure, kidney diseases, heart failure, panceratitis, diabetes and the lack of consent by family in any step of the study. This was a pilot study, 13 patients entered in each group. Sample size increased to 16 patients in each group with calculation of 20% slump(power 80% &α of 0/05) Consent form was taken from the closest family member, in the first contact with the patient's family. We controlled provoking factors for hypoglycemia such as interruption of minimal diet feedings, interruption of a source of intravenous dextrose, time of serum infusion about dextrose, intra lipid and amino acid, exclude date of glucometer kits, nursing care with exact time of blood glucose checking.

Randomization

Patients were assigned randomly by sealed envelop, to receive either IIT [steady insulin infusion with cessation in BS<4.2 mmol/l (<75mg/dl) until 2 hour] or CGC[subcutaneous insulin infusion if BS>6.1 mmol/l (>180 mg/dl)] in the ICU.

Data collection

At baseline, data on demographic and clinical characteristics including information about the age, sex, ideal body weight, percent of parenteral nutrition, percent of enteral nutrition, amount of blood glucose and GCS in admission to the study, amount of dextrose, intra lipid and amino acid infusion, Acute Physiology

and Chronic Health Evaluation(APACHEII) system, data and information about concomitant diseases(infections, hospital pneumonia, acute renal failure, use and length of mechanical ventilation) were collected. Parentral nutrition was stopped when they no longer needed parenteral support. Blood samples were collected on the afternoon of admission day to the study on days 7, 10 and 14 after intervention. We collected the blood samples before antibiotic therapy. Five ml of blood samples in 50 cc TSB (Trypticase Soy Broth) was infused in thirty minutes intervals. Samples were incubated 24-48 hours in incubator and then pathogens were cultured from incubated blood samples.

Diagnostic criteria for medical complications were specifically recorded as follow: pneumonia (temperature above 38.5°C, white blood count above 12×10000, positive blood culture); acute renal failure (defined as either a level of serum creatinine twice that present on admission to the ICU or a peak level of creatinine of>2.5 mg/dl); Sever hypoglycemic episodes (defined as blood glucose level under 40 mg/dl).Twenty eight days follow up regarding dead or alive was performed. Non of patients had pneumonia or acute renal failure on admission to the study.

Parenteral nutrition

Ideal body weight was measured with the ulna length measures. Amount of dextrose, intra lipid, amino acid, water soluble vitamins and minerals were calculated for each patient. Dextrose was infused for 8-10 hours, intra lipid for 6 hours and amino acid for 4 hours. Vitamin and minerals were injected through normal saline serum. Fluid load was assessed and controlled for each patient. To preserve the gut function, minimal diet from original Ferrosubin was prescribed for patients.

Glycemic control protocol

In the intensive insulin treatment group, 50unit insulin regular in 50cc normal saline (N/S) was prepared and infusion was started depends on the first blood glucose. If blood glucose fellunder 4.2 mmol/l (75 mg/dl), infusion was stopped for 2 hours and a second test was done 2 hours later, then infusion started if blood glucose was raised above 4.2 mmol/l (75 mg/dl). Blood glucose was measured each 2 hours in this group (table 1). Patients on CGC had serial blood glucose checks at 12 hours intervals and goal directed subcutaneous regular insulin injections to maintain blood glucose below 6.1mmol/l (180 mg/dl). Blood glucose was measured in capillary blood using IME-DC glucometer. For quality control, venous blood samples were sent to the hospital laboratory to check blood glucose levels on admission and daily during the study period of most patients. Intensive insulin treatment was maintained until discharge from the ICU. In our study all the patients received manitol, corticosteroid drugs, lasix, phenytoin and dilantin as prescribed by neurosurgeon that had hyperglycemic effects.In fact, a minimal change exists in this protocol. In insulin sliding scale that exists in Lester Hospital, in the blood glucose between 1-4.2 mmol/l, infusion is pursued.

Data analysis

Data were analyzed according to intention to treat. Continuous variables were analyzed using the Mann-Whitney rank-sum tests (nonparametric distribution). Results were displayed as mean± SD and median plus interquartile range, respectively. For comparison of variations and their trends in each group, cross-tab test and independent t-test were used.

Results

In this study 29 patients randomly assigned to one of the two treatment groups: 13 patients in IIT and 16 patients in CGC. Of 13 patients

Table 1. Insulin sliding scale chart for head trauma patients in an Iranian intensive care unit

Blood glucose mmol/l (mg/dl)	Insulin sliding scale rate (ml/hr)
< 4.2 (75)	dissection
4.2-6.8 (75-124)	1
6.9– 11 (125-199)	2
11.1 – 14.9 (200-269)	3
15 – 20 (270-360)	4
>20 (>360)	6 and call doctor to review scale

initially allocated to IIT, any of them excluded and all patients pursued until 14 days. Of 16 patients that participated in this study, three of them were expired on 5 days.

The two groups were similar with the respect to severity of injury, age and glucose values on admission day (table 2). All of the patients were men. The mean blood glucose on admission day in IIT group was 204.5± 66 mg/dl and in CGC group was 194± 52 mg/dl. The mean percent of parenteral nutrition in IIT group was 86.7± 7 and in CGC was 85.5± 7. Criteria for parenteral nutrition support of 29 patients with severe traumatic brain injury and subtypes of brain injury were shown in table 3 and 4. During the study period, no episode of hypoglycemia was associated with typical signs and symptoms of hypoglycemia, including seizures and hemodynamic instability or blood glucose under 40 mg/dl in glucometer observed. We controlled provoking factors for hypoglycemia such as inter-

Table2. Baseline characteristics of 29 patients with severe traumatic brain injury

Variable	IIT group	CGC group	P value
	Mean± SD	Mean± SD	
Number	13	16	
Age(years)	31±11	36.6±13	0.27
APACHEII score	13.4±2	12.6± 3	0.08
Ideal body weight(kg)	71.6±6.5	72.2±7	0.83
Glascow coma scale (GCS)	7.3±1	8.4±2	0.14
Blood glucose on admission(mg/dl)	204.5±66	194±52	0.66
Parenteral nutrition(% intake)	86.7 ±7	85.5±7	0.60
Dextrose(ml)	777±268	912.5±206	0.13
Intra lipid(ml)	808±194	812.5±214	0.90
Amino acid(ml)	615±219	625±223	0.90
Enteral nutrition(% intake)	13.3 ± 7	14.5 ± 7	0.60

Table 3.Criteria for parenteral nutrition support of 29 patients with severe traumatic brain injury

Criteria for parenteral support	IIT group		CGC group	
	number	percent	number	percent
Residue	3	23	4	25
Residue+ diarrhea	3	23	0	0
Diarrhea+ muscle erosion	7	53.8	9	56.3
Residue+ muscle erosion	0	0	3	18.8

P value=0.185

Table 4. Subtypes of brain injury in 29 patients with severe traumatic brain injury

Criteria for parenteral support	IIT group		CGC group	
	number	percent	number	percent
SAH(subarachnoid hemorrhage)	3	23	1	6
SDH (subdural hemorrhage)	1	7.7	4	25
Contusion	2	15.4	4	25
IVH(intraventricular hemorrhage)	2	15.4	3	18.8
CT normal	5	38.5	4	25

X2 test (P value= 0.12)

Table 5. Comparison of blood culture test within groups on intervention days

Blood culture	IIT group		CGC group		P value
	number	Percent	number	percent	
Positive (admission)	3	23.1	2	12.5	0.45
Negative (admission)	10	76.9	14	87.5	
Positive (day 7)	2	15.4	5	38.5	0.18
Negative (day7)	11	84.6	8	61.5	
Positive (day 10)	2	15.4	5	38.5	0.18
Negative (day 10)	11	84.6	8	61.5	
Positive (day 14)	2	15.4	6	46.2	0.08
Negative (day 14)	11	84.6	7	53.8	

ruption of minimal diet feedings, interruption of a source of intravenous dextrose, time of serum infusion about dextrose, intra lipid and amino-acid, exclude date of glucometer kits, nursing care with exact time of blood glucose checking. During the study period, no episode of hypoglycemia was associated with typical sign and symptoms of hypoglycemia, including seizures and hemodynamic instability or blood glucose under 40 mg/dl in glucometer observed. Pathogen growth was increased in conventional group but decreased in tight control group (not significant) (table 5).

Discussion

This randomized control trial of tight insulin treatment in which patients with brain trauma that received at least 50% of nutritional needs from parenteral rout, showed benefit in terms of pathogen growth with blood culture tests. In another studies about parenteral nutrition, one of the parenteral nutrition complications is pathogen growth that is related to hyperglycemia or catheter. In this study we tried to collect blood samples before starting antibiotic therapy to prevent false negative results. Results of this study showed no significant difference between two groups in pathogen growth during interventions. In conventional group, pathogen growth was increased due to the hyperglycemia but in intensive group, with the control of blood sugar, pathogen growth was not significantly different. Brunkhorst FM et alassessed Intensive insulin therapy and pentastarch resuscitation in severe sepsis (10).The trial was stopped early for safety reasons. Among 537 patients who could be evaluated, the mean morning blood glucose level was lower in the intensive-therapy group (112 mg per deciliter [6.2 mmol per liter]) than in the conventional-therapy group (151 mg per deciliter [8.4 mmol per liter], P<0.001). However, at 28

days, there was no significant difference between the two groups in the rate of death or the mean score for organ failure. In addition in the study by ArianeCoester, IIT did not improve the neurologic outcome of patients with STBI (sever traumatic Brain Injury) and didn't affect on sepsis and pathogen growth, but did increase the risk of hypoglycemia compared with CGT (11). Advantages of this study were homogenous patients, accurate blood glucose checking and accurate nursing care. In addition, in this study almost all the nutritional needs (>80%) were from parenteral nutrition. But low sample size and duration of hospitalization until start of study were the limitations of the study. Hyperglycemic drugs were considered on admission day but following the changes in these drugs was not assessed. Although, in this study we did not observe significant difference between two groups in pathogen growth (perhaps due to low sample size), but trend of pathogen growth was declined in tight control group. For the future researches,we suggest increasing of sample size and preparing of new scale. In addition apply of this protocol specially in all hyperglycemic patients is suggested.

Conclusions

In our study, IIT reduced pathogen growth without hypoglycemic episodes in head trauma patients.

Acknowledgments

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