INTENSIVE INSULIN THERAPY VERSUS CONVENTIONAL INSULIN THERAPY FOR CRITICALLY ILL TRAUMA PATIENTS ADMITTED TO ICU

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Abstract

Purpose: The objective of our study was to evaluate the beneficial effect of IIT in reducing mortality and morbidity in critically ill trauma patients admitted to ICU.

Method and Material

Nested cohort study within a Randomized Controlled Trial. All trauma patients with GCS ≤9 included in the original trial were included in this study. Primary outcome was ICU mortality.

Result

There was no difference in ICU mortality between IIT and CIT groups (6.5% vs. 5.5%, p = 0.67). After adjustment for baseline characteristics, IIT therapy was also not associated with mortality (Adjusted Hazard Ratio 1.33, 95% CI 0.35-5.05). IIT therapy was associated with a significant increase in the incidence of hypoglycemia as compared to CIT, at least one hypoglycemia episode occurred in 18.5% of patients in IIT and 1.3% in the CIT group (P <0.0001).

Conclusion

IIT was not associated with survival improvement in trauma patients admitted to ICU and was associated with increased incidence of hypoglycemia.

Key words: Insulin, Trauma, Intensive Care Unit, Mortality, Sepsis, Hyperglycemia, Intensive Insulin**.**

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Background

Acute hyperglycemia caused by acute disease is associated with adverse outcome which has been demonstrated in patients suffering from trauma[1]. Hyperglycemia is frequent during acute brain injury and is associated with increased mortality and morbidity[2]. Some studies have showed improvement in outcome after strict treatment of hyperglycemia in the Intensive Care Unit (ICU). Since Van den Berghe et al[3]. Published a randomized clinical trail (RCT) of critically ill surgical ICU patients and showed that intensive insulin therapy (IIT), significantly reduced in-hospital mortality. However, the beneficial effects could not be reproduced in other studies[4]. The same authors published another RCT in medical ICU and found no overall reduction in mortalty[5]. Moreover, Recent Meta-analyses showed IIT is not associated with significantly reduced mortality but is associated with an increased risk of hypoglycemia, trauma patients were not addressed in the anaylasis[6,7]. In NICE-Sugar study[8] subgroup analysis on trauma patients demonstrated a trend towards better outcome for patients with trauma as compared with those without trauma. Despite conflicting evidence, IIT has been recommended as the standard of care for critically ill patients by many associations and other professional organization[6]. Because few interventions in critically ill patients reduce mortality, the results of this trail were enthusiastically received and rapidly incorporated into guidelines[7]. A consistent finding in trials of IIT has been an increased risk of hypoglycemia, which was the main reason for termination of several clinical trials[9]. Since then, questions have been raised about the efficacy in general and in specific subgroups and about the safety of this therapy with regard to potential harm of brief hypoglycemic episodes and of high-dose insulin administration[10]. However, currently no prospective trials have been conducted in trauma ICU patients to evaluate the influence of IIT[1,3], and trauma patients only made up small proportion of the studied populations[11].

The objective of our study was to evaluate the beneficial effect of IIT in reducing mortality and morbidity in critically ill trauma patients admitted to ICU.

Methods

Setting and Patients

We carried out a nested cohort study within a randomized clinical trial carried out in a 21 bed, medical and surgical ICU in an 800- bed tertiary care teaching hospital in Riyadh, Saudi Arabia. This ICU is closed unit, run by in-house full-time board-certified intensivists, with more than a thousand admissions per year of whom 17% of admission to ICU are trauma. Details of the RCT[12] are published elsewhere. Briefly, the objective of the original RCT was to assess the effect of IIT among medical- surgical ICU patients. 523 patients were allocated to either intensive or conventional insulin therapy (CIT), we found that IIT was not associated with improved survival among ICU patients and was associated with increased occurrence of hypoglycaemia in IIT(28.6% vs. 3.1% of patients; P 0.0001).

The current study included patients who had trauma, ≥18 years and had serum glucose level as measured by the laboratory >6.1 mmol/L during the first 24 hours of ICU admission.

Interventions

IIT was aimed to blood glucose levels between 4.4 to 6.1 mmol/L (80-110 mg/dl). In conventional insulin therapy, insulin infusion was adjusted to maintain a blood glucose level of 10.0-11.1 mmol/L (180-200 mg/dL).

Measurements

The following data were collected on trauma patients: baseline demographics including gender, age. Acute Physiology and Chronic Health Evaluation II (APACHE II) scores[13], Injury Severity Score (ISS)[14], Sequential Organ Failure Assessment (SOFA)[15], intensive care unit (ICU) length of stay (LOS) was calculated as number of calendar days of ICU stay as well the hospital LOS. Patients were followed until discharge from the hospital or death whichever occurred first.

The primary end point of the study was ICU mortality. Secondary end points included hospital

mortality, ICU length of stay (LOS), hospital LOS and incidence of hypoglycemia (defined as blood glucose ≤2.2 mmol/L), mechanical ventilation duration, packed red blood cell transfusion and new renal replacement therapy (RRT), cause of death.

Statistical Analysis

Categorical data were summarized by calculating the number and the percent, whereas the continuous ones were presented as mean and standard deviation (SD). Comparison between the two groups was done using the T-test and the Chi-square test as appropriate. To adjust for the effect of potentially confounding variables, we carried out multivariate Cox regression analyses, where the following variables were included in the model: age, sex, body mass index (BMI), admission category (non-operative versus post-operative), APACHE II, SOFA, history of diabetes, inclusion blood glucose, time to randomization, vasopressor use, mechanical ventilation, sepsis, traumatic brain injury, creatinine, PaO2:FiO2 ratio, platelet count, bilirubin, GCS, and INR. The results were expressed as Adjusted Hazard Ratios (AHR) and 95% Confidence Intervals

Table 1
Baseline characteristics of in patients who received the intensive insulin therapy (IIT) and the conventional insulin therapy (CIT)

	Intensive Insulin Therapy	Conventional Insulin Therapy	P
	N=108	N= 80	
Age, mean ± SD, years	31.74 ±15.5	34.94 ±18	0.19
Female gender, No. (%)	9 (8.3%)	9 (11.25%)	0.5
BMI, mean ± SD	26.2± 6	26.8 ±7.4	0.54
ICU admission category, No. (%)			
Post-Operative	28 (25.9%)	20 (25%)	0.89
Non-Operative	80 (74. %)	60 (75%)	
APACHE II, mean ± SD	19.1± 6.6	18.7 ±7.2	0.71
SOFA, mean ± SD	8.5± 3.	8.5± 3.1	0.95
History of diabetes, No. (%)	4(3.7%)	12(15%)	0.06
Inclusion blood glucose, mean ± SD, mmol/L *	9.4± 3.1	10.1 ±3.8	0.16
Time to randomization, mean ± SD, hours	11± 7	8.9 ±7.5	0.06
Mechanically ventilated, No. (%)	103 (95.4%)	76 (95.0%)	0.91
Vasopressors, No. (%)	71 (65.7%)	51 (63.8%)	0.78
Creatinine, mean ± SD, µmol/L *	100.2± 95.7	114.1 ±117.2	0.37
Platelet count, mean ± SD, $X10^9$ / L *	169.± 94.4	183.3± 92.2	0.31
Bilirubin, mean ± SD, µmol / L	22.7 ±14.7	22.3 ±18.4	0.87
INR, mean ± SD	1.4 ±.86	1.3± 0.3	0.09
PaO_2:FiO_2 Ratio, mean ± SD	245± 121	244± 109.	0.95
GCS, mean ± SD	7.7 ±4.2	8± 4	0.66
Injury Severity Score (ISS)	26.8 ±12.6	26.9 ±12.3	0.96
Type of injury			
Brain	39 (48.8%)	55 (69%)	0.77
Chest	42 (52.5%)	65 (60.2%)	0.29
Abdomen	14 (17.5%)	22 (20.4%)	0.62
Orthopedic/soft tissue	32 (40%)	63 (56.3%)	0,01
vascular	3 (3.8%)	5 (4.6%)	0.77
Spine	21 (26.3)	17 (15.7%)	0.07

SD: Standard Deviation, BMI: Body Mass Index, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment, INR: International Normalized Ratio; PaO2:FiO2 Ratio: the ratio of partial pressure of oxygen to the fraction of inspired oxygen; GCS: Glasgow Coma Scale.
* To convert to conventional units in mg/dL, divide by 0.0555 for glucose, 88.4 for Creatinine, and 17.1 for bilirubin.

(CI). Moreover, we constructed Kaplan Meier survival curves and p-values were calculated using log rank test. Statistical significance was defined as p-value of ≤0.05. Statistical analyses were performed using the Statistical Analysis Software (SAS, Release 8, SAS Institute Inc., Cary, NC, 1999, USA).

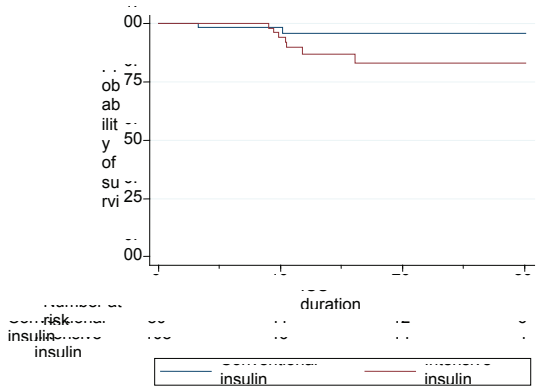
Results

During the study period, 188 patients (35.9%) were admitted to ICU with trauma. Table 1 summarizes the baseline characteristics of patients in the IIT and CIT groups. Patients in the IIT (n = 108) and CIT group (n = 80) were similar in baseline characteristics including age, gender, APACHE II, SOFA, history of diabetes and use of vasopressors. Also, post-operative ICU admission was similar in both groups as well as the history of diabetes on admission to ICU. There was no significant difference in the Injury Severity Score between IIT and CIT groups (26.8% vs. 26.9%, P = 0.96). The majority of trauma patients admitted to ICU was due to brain trauma and was similar in both groups (48.8% vs. 69%, P = 0.77). The other types of trauma were similar between the two groups except in orthopedic injury which was more in the CIT group (58.3% vs. 40%, P = 0.01).

Intervention

Table 2 presents the daily insulin, average blood glucose and caloric intake in both groups. Average daily insulin dose throughout the study period was 74.17 units in the IIT group and 10.29 units in the CIT group (P = 0.0001). Caloric intake was similar in both groups (figure 1).

Fig. 1
Kaplain Meir survival curves for intensive insulin therapy (IIT) and Conventional insulin therapy (CIP)



p-value = 0.42

Mortality

There was no difference in ICU mortality between IIT and CIT groups (6.5% vs. 5.5%, p = 0.67). After adjustment for baseline characteristics, IIT therapy was not associated with mortality difference (Adjusted Hazard Ratio = 1.33, 95% CI 0.35-5.05).

Table 3 summarizes the mortality analyses stratified by baseline characteristics.

Figure 2 shows the Kaplan-Meier survival curve for IIT vs. CIT where no difference as Observed (P = 0.42).

Hypoglycemia

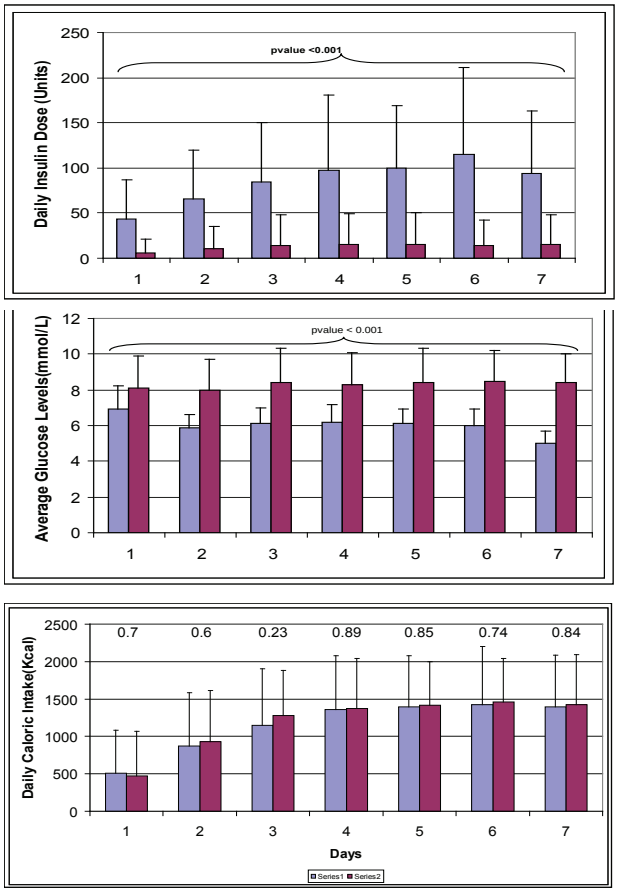
IIT therapy was associated with a significant increase in the incidence of hypoglycemia as compared to CIT, at least one hypoglycemia episode occurred in 18.5% of patients in IIT and 1.3% in the CIT group (P <0.0001).

Table 2
Insulin, glucose, and caloric intake data in patients who received the intensive insulin therapy (IIT) and the conventional insulin therapy (CIT)

	Intensive Insulin Therapy N= 108	Conventional Insulin Therapy N= 80	P
Received insulin, No. (%)	105 (97.2%)	33 (41.3%)	0.0001
Average insulin daily dose*, mean ± SD, units	74.17 ± 44.83	10.29 ±19.91	0.0001
Average glucose levels*$, mean ± SD, mmol/L	6.12 ± 0.54	8.14 ±1.36	0.0001
Average daily caloric intake**, mean ± SD, kcal	1003.85 ± 531.12	1062.34 ± 507.04	0.45
Average daily protein intake**, mean ± SD, kcal	35.19 ± 25.47	39.32 ± 25.63	0.27

SD: Standard Deviation * Calculated for all ICU stay.
$ To convert to conventional units in mg/dL, divide by 0.0555 for glucose.
** Calculated for study day 1 to 7

Figure 2: Daily insulin doses, average glucose levels and daily caloric intake from day 1 to 7 expressed as means and standard deviations. The figures shows that intensive insulin therapy (IIT) group had higher insulin doses, lower glucose levels and similar caloric intake compared with the conventional insulin therapy (CIT) group



Secondary Endpoints

There were no differences in the cause of death between the two groups. In addition, there were no differences in hospital mortality, ICU or hospital LOS. Similarly, there were no differences in mechanical ventilation duration, RBC transfusion, new renal replacement therapy or need for tracheotomy (Table 4).

Discussion

Our study showed that IIT was not associated with a reduction in ICU mortality (6.48%vs. 5.5%, P = 0.67) or hospital mortality or any of the secondary end points in trauma patients admitted to ICU. On the other hand, IIT was associated with a significant increase in hypoglycemia episode (18.5% in IIT vs 1.3% in the CIT group (P <0.0001)). Jeremitsky et al[16]. Conducted a retrospective analysis in trauma ICU on 77 patients with severe traumatic brain injury who survived more than 5 days and found that early hyperglycemia is associated with poor outcomes for patients with severe traumatic brain injury. A 12-year retrospective study was performed at surgical ICU and found that the relation of hyperglycemia and mortality is more pronounced in trauma patients[11]. These observational studies have been limited by their study design. These studies have demonstrated the association of hyperglycemia with adverse outcome in trauma patients admitted to ICU.

This association has led to a natural question to whether IIT would improve patients' outcome[17]. Billotta et al[2]. conducted a randomized trial on 97 patients with severe traumatic brain injury. Patients were randomized to intensive insulin therapy with target blood glucose of 4.44-6.66 mmol/L or conventional insulin therapy with target blood glucose below 12.22 mmol/L. They found that both groups had similar mortality and neurological outcomes, even though with the use of insulin to keep blood glucose less than 12.2 mmol/L in the conventional group the incidence of hypoglycemia were higher than our finding (100% vs. 18.3%) but they used blood glucose level less than 4.4 mmol/l as definition of hypoglycemia. NICE-SUGAR published recently[8] involved 6104 patients randomized to IIT or conventional insulin therapy, they found Intensive glucose control increased mortality among adults in the ICU. In subgroup-specific treatment effects for patients with trauma [41/421 vs. 57/465 (odds ratio for death 0.77 (0.50-1.18 (p = 0.07)] as compared with those without trauma indicated a possible trend toward treatment effects for patients with trauma, in addition to patients in our 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.

Another randomized prospective trial[1]conducted of intensive vs. conservative insulin on patients admitted to ICU after intracranial aneurysm clipping in patients with SAH. They enrolled 78 patients and found mortality and neurological outcome or vasospasms were not affected by intensive insulin therapy.

Table 3

ICU mortality in the intensive insulin therapy (IIT) and the conventional insulin therapy (CIT) groups and the results of Cox proportional stepwise multivariate analysis

	Intensive Insulin Therapy	Conventional Insulin Therapy	Adjusted Hazard Ratio (AHR)	95% Confidence Interval (95% CI)	*P*
	n =108	n = 80			
ICU mortality, No. (%)	7 (6.5%)	4 (5%)	1.33	0.35 - 5.05	0.67
Stratified By:					
Age in yrs					
≤ 29	4/57 (7.0%)	1/38 (2.6%)	3.52	0.39 - 31.47	0.26
> 29	3/51 (5.9%)	3/42 (7.1%)	1.19	0.19 -7.61	0.86
Gender					
Male	5/99(5.1%)	4/71 (5.6%)	1.67	0.35 - 8.05	0.52
Female	2/9 (22.2%)	0 (0%)			
Admission category					
Post-Operative	2/28 (7.1%)	1/20 (5.0%)	1.27	0.12 -14.10	0.84
Non-Operative	5/80 (6.3%)	3/60 (5.0%)	1.93	0.38 - 9.8	0.43
APACHE II					
≤ 18	0 (0%)	0 (0%)			
> 18	7/54 (12.6%)	4/60 (11.1%)	1.85	0.5 - 6.86	0.36
GCS					
≤ 7	5/63 (7.9%)	2/45 (4.4%)	1.45	0.27 -7.86	0.67
> 7	2/45 (4.4%)	2/35 (5.7%)	1.17	0.15 - 8.86	0.88
SOFA					
≤ 9	3/69(4.4%)	1/44(2.3%)	1.78	0.17-18.51	0.63
> 9	4/39 (10.3%)	3/36 (8.3%)	0.33	0.03 -3.86	0.38
History of diabetes					
Yes	0	1/12 (8.3%)			
No	7/104 (6.7%)	3/68 (4.4%)	1.44	0.37-5.62	0.6
Inclusion blood glucose ●					
≤ 8.9 mmol/L	1/56 (1.8%)	1/39(2.6%)	0.84	0.05 -13.52	0.9
> 8.9 mmol/L	6/52 (11.5%)	3/41(7.3%)	1.67	0.36 -7.7	0.51
Vasopressor therapy					
Yes	7/71 (9.9%)	3/51 (5.9%)	1.49	0.34 - 6.57	0.6
No	0	1/29 (3.5%)			
Traumatic brain injury					
Yes	2/55(3.6%)	1/39(2.5%)	1.58	0.14 -17.4	0.71
No	5/53(9.4%)	3/41(7.5%)	2.63	0.56 -12.37	0.22
ISS					
≤ 26.5	2/51(3.9%)	1/42 (2.3%)			0.9
> 26.5	5/57(8.8%)	3(11.1%)	1.76	0.33 - 9.29	0.51

* AHR and 95% CI could not be calculated due to small numbers. BMI: Body Mass Index, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment, INR: International Normalized Ratio; PaO2:FiO2 Ratio: the ratio of partial pressure of oxygen to the fraction of inspired oxygen; GCS: Glasgow Coma Scale; ISS: Injury Severity Score.

● To convert to conventional units in mg/dL, divide by 0.0555 for glucose.

Table 4
Secondary end points in the intensive insulin therapy (IIT) and the conventional insulin therapy (CIT)

	Intensive Insulin Therapy n=108	Conventional Insulin Therapy n=80	*P*
Causes of death			
Multi-organ failure	2(1.9%)	1(1.3%)	1.0
Brain death	5 (4.6%)	2(2.5%)	0.7
Other causes	0 (0%)	1(1.3%)	0.43
Hospital mortality	10 (9.3%)	13 (16.3%)	0.15
ICU LOS, mean ± SD, days	10±8 8.0	12.6± 11.8	0.18
Hospital LOS, mean ± SD, days	65.4 ±188.8	76.4± 99.9	0.42
Hypoglycemia			
Number of patients	20 (18.5%)	1 (1.3%)	0.0001
Rate of hypoglycemias/100 treatment days			
Mechanical ventilation duration, mean ± SD, days	9.8 ±7.5	11.8 ±10.2	0.14
PRBC transfusion, mean ± SD, units	1.79± 4.8	1.9 ±3.7	0.84
New renal replacement therapy, No. (%)	5 (4.6%)	5 (6.3%)	0.75
Tracheotomy	30(27.8%)	26(32.5%)	0.52

LOS: Length of Stay, PRBC: Packed Red Blood Cell, SD: Standard Deviation

In concordance with our finding Van den Berghe et al[18] reported a sub group analysis of RCT conducted in surgical ICU patients with isolated brain injury, majority of patients were non trauma, showed ICU mortality (18% in intensive insulin group vs. 23%, in the conventional group, p = 0.6) and was not affected by the intensive insulin, as well as hospital mortality was not affected[18].

Possible explanation for the lack of benefit of IIT includes the increased risk of hypoglycemia. The incidence of hypoglycemia in our trial was 18.5% in the IIT nearly similar to a recent meta-analysis[6] which showed pooled incidence of 14.1%. Although there is no consensus of the definition of hypoglycemia, we conservatively defined hypoglycemia as a glucose level ≤2.2 mmol/L (40 mg/dL physiologic changes, with increased levels of counter regulatory hormones, occur at a glucose level of approximately 3.6 mmol/L (65 mg/dL), adrenergic symptoms at approximately 31 mmol/L (55 mg/dL), and cognitive dysfunction at approximately 2.5 mmol/L (45 mg/dL)[19]. Nevertheless, prevention and early detection of hypoglycemia need to be a major concern when implementing this therapy [20]. Continuous glucose-monitoring systems are awaited, which could further reduce episodes of hypoglycemia however, their clinical impact is still unknown. Hypoglycemia is associated with an increased risk of death and this increased risk may have been related to undiagnosed episodes of hypoglycemia at the earlier phase of the stay in the ICU in patients who were unconscious or comatosed. Another possible explanation is the effect of tight blood glucose on brain metabolism. Oddo et al conducted retrospective analysis of a prospective observational cohort monitored brain tissue markers of glucose metabolism for patients admitted to neurological ICU with severe brain injury and found insulin-induced reduction of systemic glucose concentration was associated with significant impairment in cerebral glucose metabolism. Tight systemic glucose control (4.4-6.7 mmol/L) was associated with increased prevalence of critical brain tissue glycopenia and energy crisis when compared with a less restrictive systemic glucose range (6.8-10 mmol/L) which correlated with increased mortality. IIT may impair cerebral glucose metabolism after severe brain injury[22].

Strengths of this study include the prospective data collection as part of a randomized controlled trial. Furthermore, the ICU operated under a closed-system staffed mainly by critical care board-certified intensivists, thus increasing the homogeneity of clinical management and controlling for unknown variables. Our study had several limitations: it was a post hoc observational study conducted at a single institution and the unblinded nature of the intervention.

Conclusion

IIT was not associated with survival improvement in trauma patients admitted to ICU and was associated with increased incidence of hypoglycemia. We believe that our data about the relation between IIT and clinical outcomes on trauma patients may pave the way for more RCT studies on trauma patients admitted to ICU which might shed more light on the real impact of IIT on clinically relevant outcomes. With the lack of demonstrated benefit and the increased risk of hypoglycemia, we do not advocate controlling blood glucose to the levels used in IIT in trauma patients.

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