Arq Neuropsiquiatr 2007;65(3-B):733-738

INTENSIVE INSULIN THERAPY VERSUS CONVENTIONAL GLYCEMIC CONTROL IN PATIENTS WITH ACUTE NEUROLOGICAL INJURY

A prospective controlled trial

José Raimundo A. de Azevedo[1], Eduardo Rodrigues M. Lima[2], Rachel Jorge Dino Cossetti[2], Renato Palácio de Azevedo[2]

ABSTRACT - *Objective:* To compare intensive insulin therapy to conventional glycemic control in patients with acute neurological injury evaluating neurological outcome and morbimortality. *Method:* Patients with two glycemias above 150 mg/dL 12 hours after admission were randomized to receive intensive insulin therapy (G1) or conventional treatment (G2). We evaluated a subgroup of patients with acute brain injury from July, 2004 to June, 2006. *Results:* G1 patients (n=31) received 70.5 (45.1-87.5) units of insulin/day while G2 patients (n=19) received 2 (0.6–14.1) units/day (p<0.0001). The median glycemia was comparable in both groups (p=0.16). Hypoglycemia occurred in 2 patients (6.4%) in G1 and in 1 patient (5.8%) in G2 (p=1.0). Mortality in G1 was of 25.8% and of 35.2% in G2 (relative reduction of 27%). Neurological outcome was similar in both groups. *Conclusion*: A less strict intensive insulin therapy can reduce hypoglycemia and still maintain its benefits.

KEY WORDS: intensive care, brain injury, hyperglycemia, insulin, mortality, outcome assessment.

Insulinoterapia intensiva versus controle glicêmico em pacientes com injuria neurológica aguda: estudo prospectivo randomizado

RESUMO - *Objetivo:* Comparar insulinoterapia intensiva com controle convencional da glicemia em pacientes com injuria cerebral aguda avaliando evolução neurológica e morbimortalidade. *Método*: Pacientes com duas glicemias acima de 150 mg/dL nas primeiras 12 horas após admissão foram randomizados para insulinoterapia intensiva (Grupo 1) ou tratamento convencional (Grupo 2). Avaliamos um subgrupo de pacientes com injuria cerebral aguda admitidos de julho/2004 a junho/2006. *Resultados:* O Grupo 1 (n=31) recebeu 70,5 (45,1–87,5) unidades de insulina/dia enquanto o Grupo 2 (n=19) recebeu 2 (0,6–14,1) unidades/dia (p<0,0001). A glicemia mediana foi comparável nos dois grupos (p=0,16). Hipoglicemia ocorreu em 2 pacientes (6,4%) no Grupo 1 e em 1 paciente (5,8%) no Grupo 2. A mortalidade no Grupo 1 foi 25,8% contra 35,2% no Grupo 2 (redução relativa de 27%). A evolução neurológica foi semelhante nos dois grupos. *Conclusão:* Insulinoterapia intensiva com controle mais flexível da glicemia reduz a incidência de hipoglicemia mantendo os benefícios do tratamento.

PALAVRAS-CHAVE: tratamento intensivo, injuria cerebral, hiperglicemia, insulina, mortalidade, prognóstico.

The association of hyperglycemia and brain injury had already been described by Claude Bernard in 1849[1]. For a long time, hyperglycemia was understood only as an epiphenomenon due to the stress of an acute injury. Its impact on the neurological recovery was ignored for a long time and the increase in blood glucose level was understood as an adaptative response to provide glucose for an exclusive glucose consuming tissue. Hamilton et al.[2], in 1995, analyzing an experimental model of stroke, showed that a decrease in blood glucose levels with the use of insulin expressively reduced the extent of the ischemic injury. In 2001, Capes et al.[3], in a meta-analysis of 32 studies associating hyperglycemia on admission with the clinical outcome of patients with ischemic stroke or intracerebral hemorrhage, showed that the risk

Intensive Care Units of Hospital São Domingos and Hospital Dr. Clementino Moura. São Luis MA, Brazil: [1]Former President, Brazilian Society of Parenteral & Enteral Nutrition (2004-05) and President, Nutrition Support Committee, Brazilian Society of Intensive Care Medicine (AMIB); [2]Graduate student, Medical School, Universidade Federal do Maranhão.

Received 5 February 2007, received in final form 23 May 2007. Accepted 3 July 2007.

Dr. José Raimundo A. de Azevedo - Rua H-16 / Quadra 8 / Casa 7 / Parque Shalon - 65072-820 São Luis MA - Brasil. E-mail: jrazevedo@elo.com.br

of death during hospital stay was three times greater in patients with hyperglycemia on admission. In a previous study conducted in our service[4] we randomized 60 non-diabetic patients with acute brain injury to strict blood glucose control or to a control group. We showed that the prognosis assessed by the Glasgow Outcome Scale (GOS) was expressively better in the treatment group. Many recent studies have shown that patients with stroke treated with thrombolitics presented with high rate of unfavorable results when blood glucose was higher than 140 mg/dL before the infusion of thrombolitics[5-7].

With the publication of Van den Berghe's study[8], in 2001, demonstrating important benefits of the use of intensive insulin therapy in critically ill patients, besides other various experimental studies[2,9,10] demonstrating a reduction of the brain injury extension and a recovery of the penumbra area with a reduction of blood glucose levels with the use of exogenous insulin, there was great interest for the use of insulin therapy in patients with acute brain injury. In a recent study, Van den Berghe et al.[11], analyzed a subgroup of patients with primary brain injury from a study that included 1548 critically ill patients randomized to intensive insulin therapy or to conventional glycemic control. Although there was no difference in mortality, the authors showed that the group under continuous insulin infusion had lower levels of intracranial pressure, less seizures and an expressively better prognosis after 6 and 12 months of hospital discharge.

In July of 2004, we started a prospective randomized study including all patients with hyperglycemia on Intensive Care Unite (ICU) admission. We compared intensive insulin therapy to conventional blood glucose control. In June 30th, 2006, 260 patients had been enrolled in the study. Forty-eight patients had acute brain injury. The present study focuses on this subgroup of patients. Our primary end point is to compare the neurological recovery assessed by the Extended Glasgow Outcome Scale (GOSE) applied at least 3 months after hospital discharge. The secondary end points are ICU mortality and length of stay, occurrence of seizures and infectious complications.

METHOD

This study analyzes a subgroup of patients with acute neurological injury from the trial Intensive Insulin Therapy versus Glycemic Control in Critically Ill Patients, a prospective randomized trial that enrolled all adult, non-pregnant patients admitted to a 20-bed multidisciplinary intensive care unit of a general hospital and to an 11-bed trauma hospital ICU. We randomized all patients who presented at least two out of three glycemic level measurements in the first 12 hours of ICU admission above 150 mg/dL. After obtaining written informed consent from the relatives, the patients were randomized to one of the two study groups using envelopes. The randomization was electronically performed with the statistical program used for the data analysis. We need to emphasize that in the original trial there was no stratification for nosologies before randomization. The study protocol was approved by the Research Ethics Committee of Hospital São Domingos.

Patients randomized to Group 1 (intensive insulin therapy) received continuous intravenous insulin infusion adjusted to maintain blood glucose level between 80 e 120 mg%. The capillary glycemia was measured every two hours and insulin infusion was adjusted according to a strict protocol conducted by the nurse staff and supervised by the doctor in charge to maintain the above level of blood glucose. These patients received intravenous hydration with glucosaline solution. Nutritional therapy was initiated in the first 48 hours of ICU, preferably by the enteral route, with a formula containing 49% of carbohydrates, 16% of protein and 35% of lipids.

Patients randomized to Group 2 (glycemic control) received glucose-free intravenous hydration (Ringer 3) and enteral nutritional therapy with a formula containing 40% of carbohydrates, 16% of protein and 45% of lipids. These patients received regular insulin if blood glucose level was higher than 180 mg/dL in the measurements taken every six hours.

Although we have used isocaloric and isoproteic nutritional formulas in both groups, caloric compositions were different. In the intensive insulin therapy group we used a formula with a higher percentage of carbohydrates to attend the need for appropriate glucose intake in patients that receive intravenous infusion of regular insulin. In the glycemic control group we tried to reduce the glucose intake, either regarding the intravenous solution (Ringer 3) and the nutritional formula, objecting to reduce the role of insulin in glycemic control.

The subgroup of patients with acute neurological injury included all patients randomized between July, 2004 and June, 2006 who had an admission diagnosis of a vascular cerebral injury (hemorrhage or ischemia), brain trauma, neurological surgery or status epilepticus. Two patients had other kinds of acute brain injury: one had a cardiac arrest during anesthetic induction for an elective surgical correction of an intracerebral aneurism and the other patient was submitted to a complex endovascular procedure for an intracerebral aneurism and was admitted to the ICU with lowering of conscience level and a neurological deficit.

In this group of patients, we evaluated the outcome using the Extended Glasgow Outcome Scale[12] at least three months after hospital discharge, ICU and length of stay, seizure episodes and infectious complications (hospital acquired pneumonia, urinary tract infection and venous catheter-related infection).

Statistical analysis – Data is presented as means ± standard deviation or medians with interquartile intervals.

Fisher's exact test was used to assess categorical variables. Student's t-test was performed for continuous parametric variables and Mann-Whitney test for the non-parametric variables. All statistical tests were considered to be significant at p<0.05. SPSS version 11.0 (SPSS Inc, Chicago, IL, USA) was used for all analyses.

RESULTS

From a total of 206 patients enrolled in the trial from June, 2004 to July, 2006, 48 patients had acute neurological injury. In this subgroup 31 patients were randomized to Group 1 (intensive insulin therapy) and 17 to Group 2 (glycemic control). Although the number of patients in each group differs due to the non-stratification per disease category in the original trial, both groups were comparable for age, sex, prevalence of diabetes, Glasgow Coma Scale on ICU admission and nosology distribution. A visual difference in APACHE III scores of 70 (48–86) for Group 1 and 53 (37,5–77) for Group 2 was not statistically significant (p=0.19). These data are presented on Table 1.

Patients in Group 1 received 70.5 (45.1–87.5) units of regular insulin per day, while patients in Group 2 received 2 (0.6–14.1) units per day (p<0.0001). The difference between the mean blood glucose level of 138.9 (125.6–174) mg/dL in Group 1 compared to 148.4 (131.5–188.6) in Group 2 did not reach statistical significance (p=0.16). Hypoglicemia (defined as blood glucose level of 40 mg/dL or less occurred

Table 1. Demographic and clinical data.

	Intensive insulin therapy n=31	Glycemic control n=17	p value
Gender (M/F)	15/16	5/12	0.2
Age (yr, mean±sd)	57.1±15.4	56.2±14.4	0.8
APACHE III			
Median	70	53	0.19
Interquartile range	48–86	37.5–77	0.16
Nosologies n (%)			
Brain ischemia/status E	13 (42)	8 (47)	
Intracerebral or SA hemorrhage	7 (22.5)	3 (17.5)	
Brain trauma	4 (13)	3 (17.5)	
Tumor / neurosurgery	5 (16)	3 (17.5)	
Others	2 (6.5)	0	
LOS (days)			
ICU			
Median	9	9	
Interquartile range	4–22	4–15.5	0.6
Hospital			
Median	19.5	15.5	
Interquartile range	7.7–39.2	4.2–21.7	0.16
GCS (mean±sd)	9.5±3.8	10.2±3.8	
Positive history of diabetes (n%)	13 (42)	6 (35.2)	0.7

GCS, Glasgow Coma Scale.

Table 2. Insulin therapy, blood glucose and hypoglycemia.

	Intensive insulin therapy n=31	Glycemic control n=17	p value
Bood glucose (m/dL)			
Median	138.9	148.4	
Interquartile range	125.6–174	131.5–188.6	0.16
Insulin dose			
IU / day / patient			
Median	70.5	2	
Interquartile range	45.1–87.5	0.6–14.1	<0,001
Hypoglycaemia n (%)	2 (6.4)	1 (5.8)	1.0

Table 3. Mortality, morbidity, outcome.

	Intensive insulin therapy n=31	Glycemic control n=17	p value
Mortality ICU n (%)	8 (25.8)	6 (35.2)	0.5
Pneumonia n (%)	9 (29.9)	3 (17.6)	0.5
UTI n (%)	3 (9.6)	1 (5.8)	1.0
Catheter-related infection n (%)	2 (6.4)	0	
Convultions	1	0	
GOSE Unfavorable evolution n (%)	9 (53)	5 (55.5)	NS

GOSE, Glasgow Outcome Scale Extended.

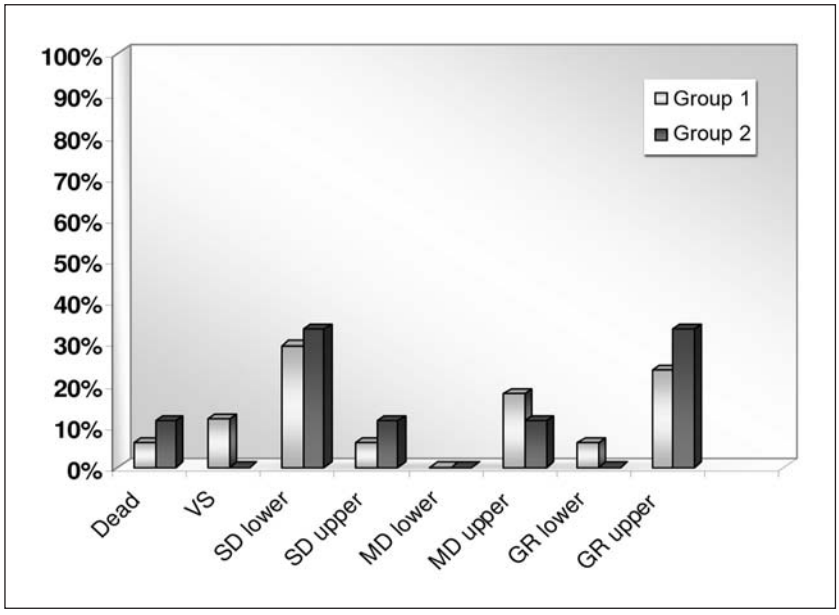

Figure. Extended Glasgow Outcome Scale. VS, vegetative state; SD, severe disability; MD, moderate disability; GR, good recovery.

in 2 patients (6.4%) in the intensive-therapy group and in 1 patient (5.8%) in the glycemic control group (p=1.0) (Table 2).

Mortality, morbidity and neurological recovery – It was observed a tendency for a lower mortality rate for patients in the intensive insulin therapy group (relative reduction of 27%) (Table 3). It was not observed significant difference for infectious complications between the two groups. The GOSE, used to evaluate the neurological recovery after hospital discharge, showed that 9 (53%) patients in Group 1 and 5 (55.5%) patients in Group 2 had an unfavorable recovery (death, vegetative state or severe disability). The GOSE was applied at a mean time of 14 months after hospital discharge in both groups (Table 3) (Figure).

DISCUSSION

Although this study has shown a tendency for a lower ICU mortality for the subgroup of patients with acute brain injury submitted to continuous intravenous insulin infusion, there was no difference between both subgroups concerning neurological recovery after hospital discharge. We should point out that this study was not intended to compare glycemic control to no glycemic control at all, but to compare two strategies of blood glucose control in critically ill patients. One strategy was the use of continuous intravenous insulin infusion to maintain blood glucose levels within a strict range of normal and the other one was based on the restriction of glucose intake (glucose-free intravenous hydration and use of the most hypoglycidic enteral nutrition available) plus subcutaneous insulin when necessary.

In their 2001 study, Van den Berghe et al.[8] showed expressive reduction in mortality and morbidity in critically ill patients when comparing strict glycemic control using continuous insulin infusion to intravenous infusion of glucose solution at 5% and nutritional formula with no glucose restrains plus the use of intravenous insulin if blood glucose achieved levels above 215 mg/dL. After various studies showing that most of the benefits of insulin therapy are due to the glycemic control itself[13,14], we understood that it would be important to compare intensive insulin therapy to glycemic control without the use of high doses of insulin.

Observing the glycemic levels in both groups of our study we can infer that we succeeded on this purpose. Patients in the intensive insulin therapy group had a median blood glucose of 138.9 mg/dL while in the control group it was of 148.4 mg/dL. To reach these values it was necessary to use 70.5 units of regular insulin per patient per day in Group 1 versus 2 units/patient/day in Group 2. We also observed that the median glycemia of Group 1 was out of the previously established range for treatment.

The severity of our patients created a great difficulty to maintain blood glucose levels always within a normal range. On the other hand, in a pilot study conducted in our service we observed that when we used the 2001 Van den Berghe's protocol[8], despite a better control of glycemic levels, we also had a higher incidence of hypoglycemia episodes. Considering this, we made some adjustments in the Leuven's protocol[8] which resulted in a less strict glycemic control but also in a lower incidence of hypoglycemia. In our study, the incidence of hypoglycemia in this subgroup of neurological patients was very low (6.4% in Group 1 and 5.8% in Group 2), which greatly differs from the incidence observed by Van den Berghe et al.[15] in a study with clinical patients (25% of hypoglycemia in the intensive insulin therapy group).

Although an association between acute injury and hyperglycemia is well known since Claude Bernard[1], Malamed et al.[16] in a retrospective study, first demonstrated that hyperglycemia occurs in an expressive percentage of patients with vascular brain injury without previous history of diabetes and also observed an association between hyperglycemia and mortality. Recent clinical studies showed great benefits of intensive insulin therapy in patients with acute myocardial infarction[17] and in critically ill patients[8]. These findings revived an interest for the possible benefits of insulin therapy in critical patients with acute neurological injury. Animal studies[2,9,10] have already shown that a reduction in blood glucose levels with the use of insulin resulted in diminished ischemic brain injury.

Capes et al.[3] in a meta-analysis of 32 studies, analyzed the impact of hyperglycemia on admission over the mortality of patients with ischemic or hemorrhagic vascular brain injury and demonstrated that hyperglycemic nondiabetic patients had a 3-fold higher mortality when compared to normoglycemic patients. Baird et al.[18] demonstrated that persistent hyperglycemia during the acute phase of a stroke resulted in an enlargement of the ischemic area, as shown by magnetic resonance images (MRI). In their conclusion, the authors emphasized the need for more prospective studies analyzing the use of intensive insulin therapy in acutely neurological injured patients.

In 2005, Van den Berghe et al.[11] published a subanalysis of a large randomized trial with 1.548 ICU patients, randomized to receive either continuous infusion of regular insulin to maintain glycemia between 80 and 110 mg/dL or conventional glycemic control, tolerating glucose levels up to 200 mg/dL. In this subgroup analysis, Van den Berghe demonstrated that 63 patients with primary brain injury (stroke, intracerebral hemorrhage, brain trauma and status epilepticus) presented clear benefits from the intensive insulin therapy due to a reduced intracranial pressure, lower incidence of seizures and a better neurological recovery when evaluated by the Karnofsky Score at 6 and 12 months after hospital discharge.

Our study, as well as Van de Berghe's study[11], analyses a subgroup of patients from a general population of a larger trial. Differently from the Leuven's study, we intended to compare patients undergoing intensive insulin therapy to patients under glycemic control without the use of high doses of insulin. Although the glycemic levels were only slightly higher in the control group, the intensive insulin therapy provided a relative reduction in mortality without increasing the risk for hypoglycemia. Despite that, the neurological recovery assessed after a mean time of 14 months after hospital discharge through the Extended Glasgow Outcome Scale was comparable for both groups.

Our study indicates a clear need for larger casuistics with specific disease categories. It also demonstrates the need to use more flexible protocols of intensive insulin therapy that allow a less strict glycemic control, like ours. With this approach, we can greatly reduce the major limitation of the intensive insulin

therapy which is the high incidence of hypoglycemic episodes and, at the same time, it enables us to maintain the benefits of the continuous insulin infusion.

REFERENCES

1. Bernard C. Chives rendus diabetiques. CR Soc Bilo (Paris) 1849;1:10.
2. Hamilton MG, Tranmer BI, Auer RN. Insulin reduction of cerebral infarction due to transient focal ischemia. J Neurosurg 1995;82:262-268.
3. Capes SE, Hunt D, Malmberg K, et al. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke 2001;32:2426-2432.
4. Azevedo JRA, Silva LGS. Prognóstico de pacientes neurológicos e neurocirúrgicos submetidos a prevenção de hiperglicemia. Rev Bras Ter Intens 1997;9:77-81.
5. Leigh R, Zaidat OO, Suri MF, et al. Predictors of hyperacute clinical worsening in ischemic stroke patients receiving thrombolitic therapy. Stroke 2004;35:1903-1907.
6. Saposnik G, Young B, Silver B, et al. Lack of improvement in patients with acute stroke after treatment with thrombolitic therapy: predictors and association with outcome. JAMA 2004;292:1839-1844.
7. Alvarez-Sabin J, Molina CA, Montaner J, et al. Effects of admission hyperglycemia on stroke outcome in reperfused tissue plasminogen activator-treated patients. Stroke 2003;34:1235-1241.
8. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359-1367.
9. Fukuoka S, Yeh H, Mandybur TI Tew JM Jr. Effect of insulin on acute experimental cerebral ischemia in gerbils. Stroke 1989;20:396-399.
10. Voll CL, Aver RN. Insulin attenuates ischemic brain damage independent of its hypoglycemic effects. J Cereb Blood Flow Metab 1991;11:1006-1014.
11. Van den Berghe G, Schoonheydt K, Becx P, Bruyninckx F, Wouters PJ. Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology 2005;64:1348-1353.
12. Wilson JTL, Pettigrew LEL, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. J Neurotrauma 1998;15:573-585.
13. Van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. Crit Care Med 2003;31:359-366.
14. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. JAMA 2003;290:2041-2047.
15. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. N Engl J Med 2006;354:449-461.
16. Melamed E. Reactive hyperglycemia in patients with acute stroke. J Neurol Sci 1976;29:267-275.
17. Malmberg K, Ryden L, Efendic S, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (digami study): effects on mortality at 1 year. J Am Coll Cardiol 1995;26:57-65.
18. Baird TA, Parsons MW, Phanh T, et al. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. Stroke 2003;34:2208-2214.