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# Insulin infusion in intensive care: randomized controlled trial*

INFUSÃO DE INSULINA EM TERAPIA INTENSIVA: ENSAIO CONTROLADO RANDOMIZADO

INFUSIÓN DE INSULINA EN CUIDADOS INTENSIVOS: ENSAYO CONTROLADO ALEATORIZADO

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**ABSTRACT**

This randomized controlled trial compared the use of an intensive and conventional insulin protocol on clinical outcomes in patients with severe sepsis and septic shock, in the first 72 hours. It was conducted at a university hospital in the city of São Paulo. Patients (n=46) were allocated into two groups: intensive glycemic (blood glucose between 80-110mg/dl) and conventional (180-220mg/dl). The Student's t-test and chi-square test were used for data analysis. A statistically significant (p<0.001) difference was observed in mean glycemia, but there was no difference in the variables of mean minimum arterial pressure (p=0.06) or maximum (p=0.11), serum creatinine (p=0,33) or in mortality (p=0.11). Although there was no difference between the groups regarding mortality, hemodynamic instability in the conventional group was longer and the only deaths occurred in it.

**DESCRIPTORS**

Infusions, intravenous
Insulin
Blood glucose
Intensive Care Units
Sepsis
Shock, septic

**RESUMO**

Ensaio clínico controlado e aleatorizado que comparou o uso de protocolo de insulina intensivo e convencional na evolução clínica de pacientes em sepse grave e choque séptico, nas primeiras 72 h. Foi conduzido em um hospital universitário na cidade de São Paulo. Os pacientes (n=46) foram alocados em dois grupos: glicêmico intensivo (glicemia entre 80-110mg/dl) e convencional (180-220mg/dl). Utilizaram-se testes t-Student e Qui-Quadrado na análise dos dados. Observou-se diferença estatisticamente significativa (p<0,001) na média glicêmica, mas não houve diferença para as variáveis pressão arterial média mínima (p=0,06) e máxima (p=0,11), creatinina sérica (p=0,33) e na mortalidade (p=0,11). Apesar de não haver diferença entre os grupos quanto à mortalidade, a instabilidade hemodinâmica no grupo convencional foi mais duradoura e somente nele ocorreram óbitos.

**DESCRITORES**

Infusões intravenosas
Insulina
Glicemia
Unidades de Terapia Intensiva
Sepse
Choque séptico

**RESUMEN**

Ensayo clínico aleatorio controlado y randomizado que comparó el uso de protocolo de insulina intensivo y convencional en la evolución clínica de pacientes en sepsis grave y shock séptico, en las primeras 72 horas. Fue realizado en un hospital universitario de la ciudad de São Paulo. Los pacientes (n=46) fueron distribuidos en dos grupos: glucémico intensivo (glucemia entre 80-110mg/dl) y convencional (180-220mg/dl). Se utilizaron tests t-Student y Chi-cuadrado para análisis de los datos. Se observó diferencia estadísticamente significativa (p<0,001) en la media glucémica, pero no hubo diferencia para las variables presión arterial mínima (p=0,06) y máxima (p=0,11), creatinina sérica (p=0,33) y en la mortalidad (p=0,11). A pesar de no existir diferencia entre los grupos en cuanto a mortalidad, la inestabilidad hemodinámica en el grupo convencional fue más duradera y sólo en él existieron decesos.

**DESCRIPTORES**

Infusiones intravenosas
Insulina
Glucemia
Unidades de Cuidados Intensivos
Sepsis
Choque séptico

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## INTRODUCTION

Hyperglycemia and insulin resistance are metabolic dysfunctions frequently observed in critical patients and occur by the action of circulating cytokines and counter-regulatory hormones released under stress conditions[1-2]. Hyperglycemia is considered potentially toxic for increasing the risks of inflammatory and thrombotic events that contribute to the occurrence of multiple organ and system dysfunction[3-4]. This event is associated with poor prognosis in diabetic and non-diabetic patients and, at hospital admission negatively affects the prognosis of non-diabetic patients with myocardial infarction[5-6].Clinical trials have demonstrated the potential benefits of insulin infusion on glycemic control in critically ill patients, regardless of the core diagnosis. The use of protocols that are designed to maintain the glycemic levels between 80-110 mg/dl presented a positive impact on clinical outcomes in critically ill patients, causing a reduction in morbidity and mortality[7-10].

A pioneering study that involved 1,548 critical surgical patients hospitalized in an intensive care unit (ICU) compared to the use of intensive insulin (maintenance of glycemia between 80-110 mg/dl) and conventional insulin (maintenance of glycemia below 216 mg/dl), through use of the Leuven protocol. The authors observed decreased morbidity and mortality, and in the intensive group there was a reduction of 41% of cases of renal insufficiency (RI), 50% of hemotransfusions and 34% of mortality[9].

Another research conducted in clinical and surgical ICU compared the clinical outcome of two groups of patients (intensive glycemic control X conventional) and showed a reduction of the occurrence of anemia, RI, length of stay in ICU and mortality of patients undergoing intensive glycemic control[10].

These promising results led the health agencies, Joint Commission on Accreditation of Healthcare Organizations and the Institute for Healthcare Improvement, to make recommendations on the implementation of glycemic control in the ICU[2]. However, subsequently the benefits of glycemic control have not been confirmed in other studies.

The NICE SUGAR, VISEP and GLUCONTROL were multicenter studies that demonstrated that intensive glycemic control elevated the risk of hypoglycemia, an aspect that was related to increase in the mortality of critical patients[11-13]. The VISEP, a study conducted with patients in severe sepsis and septic shock that adopted the protocol for intensive glycemic control, showed there was no difference in mortality (29.5% in the experimental group and 32.8% in the control group). However, it was necessary to discontinue the study due to an increase in the number of severe hypoglycemia (12.1% in the experimental group and 2.1% in the control group)[12].

In recent years some meta-analyses have been published, two of which analyzed clinical trials involving critically ill patients, whose results showed no reduction in mortality with the use of intensive glycemic control[14-15]. Thus, there was controversy in regard to the use of protocols for glycemic control, especially due to the episodes of hypoglycemia; conflicting outcomes, such as mortality, are present in the studies and the data in patients with severe sepsis and septic shock remain inconclusive.

The present study compared the use of the intensive and conventional insulin protocols on the outcomes of patients with severe sepsis and septic shock, in the first 72 hours.

## METHOD

This was a clinical study conducted in the ICU of the University Hospital of the *Universidade de São Paulo* (HU-USP), Brazil. The protocol was approved by the Committee on Ethics (protocol SISNEP CAAE: 00600.198.000-07). Those responsible for the patients signed the terms of free and informed consent.

> Clinical trials have demonstrated the potential benefits of insulin infusion on glycemic control in critically ill patients, regardless of the core diagnosis.

The sample was consecutive, that is, all patients who presented with the selection criteria were recruited, in the period of January of 2004 to December of 2006. In this manner, patients who met the following inclusion criteria participated in the study: greater than 18 years, severe sepsis or septic shock, according to the criteria defined by the Conference of the American Society of Intensive Care: temperature >38ºC or <36°C; cardiac frequency (CF)>90 bpm; respiratory frequency (RR)>20 bpm or increase in the partial pressure of carbon dioxide (PaCO2) and leukocyte count>12000 per $mm^3$[14]. Patients with cancer, Child C hepatopathy, acquired immunodeficiency syndrome, acute myocardial infarction, sepsis for more than 24 hours, and pregnant women were excluded.

Patients were randomized in the study groups by drawing lots. In each opaque envelope, previously sealed by a professional not involved in the trial, there was a flier with the description of the group, namely A – Intensive Group, whose glycemic levels should be maintained between 80-110mg/dl (normoglycemic), and B – Conventional Group, in which glycemic levels were to be between 180-220mg/d (hyperglycemic). At the time of ICU admission, the medical intensivist on duty always removed the first envelope to allocate patients into Groups A or B.

In both groups, blood collection for glycemia benchmarking was conducted through the arterial catheter. Glycemic control was performed at the time of ICU admission, every 1-2 hours until stabilization (three consecutive values in the desired value range for each group), and then the measurements were performed every four hours. Insulin 100 IU was diluted in a saline solution (100 mL), resulting in the proportion of 1ml/IU. The control of the infusion was performed by

nurses, according to the Protocol of Blood Glucose Control used in the assay.

In this ICU, composed of 11 beds, the nurse / patient relationship was 1:2, and the technician/nursing assistant:patient was close to 1:1. The process of implementation of the protocol included the participation of a nurse of reference at every turn.

Data collection occurred in the first 72 hours of patient hospitalization. Given that one review showed that the impact of the use of the intensive glycemic control protocol increases with the time of application, and the benefits may be seen after the second day of treatment[16], in the present study we opted to evaluate the patients in the first 72 hours.

We evaluated two sets of demographic and clinical variables (gender, age, type of patient, prior comorbidity such as diabetes mellitus, cardiac dysfunction in sepsis, sepsis classification, glycemia, heart rate (HR), mean arterial pressure (MAP), creatinine, urine output, and death in 72h) and therapeutic (consumption of crystalloids, insulin and catecholamines). The primary outcome analyzed was death in the first 72h.

Data were processed using the statistical package, the Statistical Package for the Social Sciences, SPSS, version 16.0. The chi-square test was used to verify the existence of differences in proportions among the groups of the variables of gender, diabetes mellitus, cardiac dysfunction and sepsis. The Fisher exact test or likelihood ratio test was used for the following variables: patient types, classification of sepsis and death. For the comparison of mean age, glycemia, intake of dobutamine, MAP and HR between the groups, the student t-test was used. For the variables related to the mean intake of noradrenaline and insulin, the nonparametric Mann-Whitney test was used. We adopted a significance level of $p<0.05$.

## RESULTS

The intensive group was composed of 21 patients and there were 25 in the conventional. In both there was a predominance of male patients (58.7%), medical (78.3%) and who presented septic shock (78.3%) (Table 1). There was no difference between groups regarding mean age (p=0.50) which was 53.8 years (SD=18.8) in the intensive group and 49.8 years (SD=20.0) in the conventional.

In the analysis of the glycemic levels, there was a significant difference in mean glycemia between groups ($p<0.001$) within 24-72hrs. In the conventional group the glycemic levels remained below the range recommended by the protocol (Table 2). There was only one episode of severe hypoglycemia (<40 mg/dL) in the intensive group. The rate of hypoglycemia compared to the total number of patients was 4.8%.

Despite the mean intake of insulin in the intensive group represented almost twice the conventional group, there was no significant difference (p=0.07) (Table 3).

**Table 1** – Distribution of patients of the intensive and conventional groups according to demographic-clinical variables

| Variables | Intensive n=21 n (%) | Conventional n=25 n (%) | Total n=46 n (%) | p-value |
|---|---|---|---|---|
| **Sex** | | | | |
| Male | 14 (66.7) | 13 (52.0) | 27 (58.7) | 0.48 |
| Female | 7 (33.3) | 12 (48.0) | 19 (41.3) | |
| **Type of patient** | | | | |
| Medical | 17 (81.0) | 19 (76.0) | 36 (78.3) | 0.73$^F$ |
| Surgical | 4 (19.0) | 6 (24.0) | 10 (21.7) | |
| **Diabetes Mellitus** | | | | |
| No | 15 (71.4) | 18 (72.0) | 33 (71.7) | 0.78 |
| Yes | 6 (28.6) | 7 (28.0) | 13 (28.3) | |
| **Cardiac dysfuntion in sepsis** | | | | |
| No | 13 (61.8) | 16 (64.0) | 29 (63.1) | 0.87 |
| Yes | 8 (38.2) | 9 (36.0) | 17 (36.9) | |
| **Acute Renal Injury** | | | | |
| Yes | 13 (61.8) | 13 (52.0) | 26 (56.5) | 0.71 |
| No | 8 (38.2) | 12 (48.0) | 20 (43.5) | |

*F*=Fisher Exact Test

**Table 2** – Distribution of the intensive and conventional groups according to glycemic control (mg/dl)

| Glycemia | Intensive (n=21) Mean (sd) | Conventional (n=25) Mean (sd) | p-value |
|---|---|---|---|
| 24h | 121.9 (35.4) | 161.4 (43.8) | |
| 48h | 112.9 (35.2) | 162.2 (40.8) | |
| 72h | 108.5 (16.7) | 165.2 (38.2) | |
| 24-72h | 114.2 (26.1) | 160.9 (35.4) | <0.001$^T$ |

T=t-test

**Table 3** – Distribution of intensive and conventional groups according to mean consumption of insulin (ml)

| Insulin | Intensive (n=21) Mean (dp) | Conventional (n=25) Mean (dp) | p-value |
|---|---|---|---|
| 24h | 88.0 (87.6) | 56.7 (69.1) | |
| 48h | 132.7 (193.1) | 58.9 (35.9) | |
| 72h | 85.1 (79.2) | 63.8 (56.8) | |
| 24-72h | 99.9 (111.0) | 54.0 (44.3) | 0.07$^M$ |

M=Mann-Withney

The mean consumption of noradrenaline, in the period of 24-72h, in the conventional group (491.6 ml) was almost double the intensive group (251.1 ml), but differences were not statistically significant (p=0.99). For dobutamine, it was observed for the same period, closeness between the averages, being 279.7 ml (SD=208.4) in the intensive group and 284.1 ml (SD=214.2) in the conventional one.

In the intensive group, there was a tendency of a higher MAP (p=0.06) and lower maximum HR, although there was no statistically significant difference (Table 4).

**Table 4** – Distribution of the intensive and conventional groups according to mean cardiac frequency (bpm) and mean arterial pressure (mmHg).

| Hemodynamics Variables | Intensive (n=21) | Conventional (n=25) | p |
|---|---|---|---|
| | Mean (sd) | Mean (sd) | |
| **Cardiac Frequency** | | | |
| **24-72h** | | | |
| Minimum | 85.2 (13.2) | 87.0 (17.8) | 0.68$^{T}$ |
| Maximum | 113.7 (14.6) | 120.9 (18.6) | 0.11$^{T}$ |
| **Arterial Pressure** | | | |
| **24-72h** | | | |
| Minimum | 71.7 (7.4) | 66.0 (12.8) | 0.06$^{T}$ |
| Maximum | 103.8 (11.3) | 99.6 (12.8) | 0.11$^{T}$ |

T=T-Test

In the two groups, evolution was observed with reduction in the serum creatinine levels and improving fluid balance, evidenced by reduced need for crystalloid volume replacement and higher urinary output in the 72h (Table 5). It was observed that 8.7% (n=4) of the study patients who died in the 72 hour period belonged to the conventional group. Those patients presented with septic shock and at least two organ dysfunctions related to the cardiovascular and renal systems.

**Table 5** – Distribution of the intensive and conventional groups according to urinary output (ml). creatinine(mg/dl) and volume of crystalloid infused (ml) at 24. 48 and 72 hours

| Variables | Intensive Mean (sd) | Conventional Mean (sd) | p-value |
|---|---|---|---|
| **24h** | | | |
| Urinary output | 2,071.7 (1,840.6) | 1,569.4 (1,233.7) | |
| Creatinine | 2.4 (2.1) | 1.8 (1.2) | |
| Crystalloid | 2,937.5 (1,208.2) | 2,900.0 (1,120.2) | |
| **48h** | | | |
| Urinary output | 1,690.0 (1,034.8) | 1,503.0 (1,279.0) | |
| Creatinine | 2.1 (1.4) | 1.7 (1.2) | |
| Crystalloid | 2,181.8 (1,914.1) | 1,694.4 (925.8) | |
| **72h** | | | |
| Urinary output | 1,919.0 (1,276.3) | 1,883.5 (1,304.9) | |
| Creatinine | 1.9 (1.3) | 1.5 (1.0) | |
| Crystalloid | 1,166.7 (930.9) | 833.3 (288.7) | |
| **24-72h** | | | |
| Urinary output | 1,895.7 (1,123.9) | 1,490.6 (1,107.0) | 0.23$^{T}$ |
| Creatinine | 2.1 (1.5) | 1.7 (1.1) | 0.33$^{T}$ |
| Crystalloid | 2,518.7 (1,056.7) | 2,203.3 (1,392.8) | 0.10$^{M}$ |

T=T-Test; M=Mann-Withney

## DISCUSSION

Participants in the intensive and conventional groups presented very similar demographic and clinical characteristics, showing that they were homogeneous, an aspect that, in a sense, can help to reduce biases related to the analysis of the outcome investigated. In both groups, there was a need for the use of insulin, indicating that hyperglycemia was a condition present in the patients, regardless of the group to which they were allocated.

Hyperglycemia in the septic patient stems from the mechanism of peripheral resistance to insulin by the action of cytokines interleukin 1 and 6 (IL-1 and 6) and the tumor necrosis factor α (TNFα), which alter the signaling pathway of insulin in the translocation of GLUT 4 (intracellular glucose transporter) into the plasma membrane. With this, the absence of glucose in insulin-dependent tissues is provoked, such as skeletal muscle, cardiac and adipose tissue. Moreover, the greater release of hyperglycemic hormones and the use of pharmaceuticals that induce hyperglycemia, among these, corticosteroids and catecholamines, contribute to a greater need for insulin infusion in patients with this clinical condition[1].

With respect to glycemic control and therapeutic insulin treatment, there was a statistically significant difference in mean glycemia between the groups (p<0.001) in the 24-72 hour period. In Brazil, a study conducted with patients undergoing cardiac surgeries identified similar glycemic means, also noting a statistically significant difference (p<0.0016) between the study groups[17]. Considering that the objective of the intensive group was to maintain glycemic levels between 80-110mg/dl, and between 180-220mg/dl in the conventional group, it can be said that the mean glycemic levels obtained in the intensive group approached the expected and the conventional group remained with results below the range recommended by the protocol. This, most probably, can be explained by the heterogeneity of the results, in which half the patients remained with glycemic levels below 180mg/dl. In addition, all patients in the intensive group received insulin at some point to maintain glycemic levels between 80-110 mg/dl, results that were confirmed by other studies[7,9,13].

Only one episode of severe hypoglycemia was observed (<40 mg/dl) during insulin infusion in the intensive group. Although the study was not designed to evaluate the safety of the protocol, the modification in the Leuven protocol performed at the initiation of the study appeared to be beneficial. Thus, the rate of hypoglycemia in relation to the total number of patients was 4.8%. Recently, multicenter studies were interrupted due to the high incidence of severe hypoglycemia (<40mg/dl) with incidences of 17% in the VISEP and 9.8% in GLUCONTROL studies[12-13].

In the present study, the low incidence of severe hypoglycemia can also be attributed to the very favorable nurse/patient ratio (1:2) for the implementation of the intensive insulin therapy protocol. The application of protocols of this nature generates a significant increase in nurse workload, with nurses

spending approximately two hours per day per patient in the ICU, and violations of the protocols are not uncommon[18-19]. Rigorous control of activities, the intense pace of work, and pressure related to time are characteristics of the process of nursing work in the ICU, and are also imperative for the safe handling of glycemic control protocols. These demands must be taken into consideration when implementing protocols for glycemic control in the ICU environment[20].

The MAP and HR were analyzed between 24 to 72 hours, a crucial period in the evolution of severe sepsis and septic shock, in which early interventions and positive responses to treatment favor the recovery of patients, avoiding the progression to multiple organ and system failure, and death [21]. In this period there was no evidence of a difference between the groups in the means of the minimum (p=0.68) or maximum (p=0.11) HR, and the minimum (p=0.06) and maximum (p=0.11) MAP. However, a trend to a higher MAP (mean MAP 71 versus 66) and a lower maximum HR (113 versus 120) was noticed in the intensive group.

Nevertheless, it is noteworthy that for the maintenance of mean pressure (>65 mmHg) in the conventional group, an increasing amount of norepinephrine was required in the same period. It is possible that intensive glycemic control contributed to the hemodynamic improvement with the need for lower consumption of vasopressors.

In severe sepsis and septic shock, peripheral insulin resistance that occurs by the action of inflammatory cytokines involves lipolysis, the mechanism by which amounts of acids in the plasma are increased, contributing to the metabolic acidosis and, consequently, blood pressure deterioration and resistance to vasoactive drugs[1]. Additionally, it has been suggested that increased synthesis of nitric oxide (NO), due to the action of mediators of the inflammatory response, may be responsible for the hypotension associated with sepsis, including the small response to vasopressor therapy.

One of the benefits of therapy with insulin and normoglycemia is the reduction of NO liberation, a vasodilator present in the vascular endothelium[22]. Considering that practically double the insulin was administered in the intensive group, when compared to the conventional group, it can be inferred that insulin may have influenced the reduction of the inflammatory response and reduced release of NO, contributing to the hemodynamic stability of the patient. Despite the fact that this finding approximated those of previous studies that have found higher consumption of insulin in the intensive group, it is essential to conduct further investigations aiming to analyze this aspect in detail.

With respect to renal function, in this study no difference was observed between the conventional and intensive groups for alterations of the Cr, the need for crystalloid volume and urinary output. However, there was a decrease in urinary output and the Cr values during the time of monitoring the patients. During the 72 hours, the amount of volume of crystalloid solution infused was also reduced. These findings should be related to the evolution of sepsis and choices of therapy on the part of the intensivists. In the study [9], with medical patients, intensive control had a positive influence on the outcome IRA.

The use of intensive and conventional glycemic control protocols did not present a statistically significant difference (p=0.11) regarding death. However, only patients in the conventional group died, resulting in four deaths. Patients who died presented septic shock and at least two organ dysfunctions related to the cardiovascular and renal systems, aspects that certainly contributed to the outcome. In septic shock, mortality increases in the presence of organ dysfunctions and can occur in short period of time[19].

Although the study suggests that both protocols have proved appropriate for the 72 hour period, especially because they did not cause hypoglycemia, the findings can not be generalized, since the sample was small and non-probabilistic.

## CONCLUSION

The groups of patients subjected to intensive and conventional glycemic control protocols showed no differences with regard to mortality. Additionally, the groups were similar regarding renal function (serum Cr, diuresis, volume of crystalloid infused) and hemodynamics (MAP and HR). The hemodynamic stability trend observed in the intensive group, with lower norepinephrine use, may be attributed to the infusion of insulin and normoglycemia. The intensive group presented lower glycemic levels (p <0.001) and deaths occurred only among patients in the conventional group.

The data suggested that intensive glycemic control tends to reduce the mortality of patients with septic shock and severe sepsis. However, further studies are still required that may, in fact, affirm or refute these findings.

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