Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 63; Numer/Number 3/2012
ISSN 0423–104X

Comparison of metformin and insulin in the control of hyperglycaemia in non-diabetic critically ill patients

Porównanie wpływu leczenia metforminą i insuliną na kontrolę glikemii u krytycznie chorych pacjentów

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Abstract

Introduction: It is accepted that preventing hyperglycaemia during critical illness while assuring adequate caloric intake can reduce mortality and morbidity. The aim of this study was to compare the metabolic effects of metformin and insulin on hyperglycaemia in ICU patients.
Methods: This double-blind randomised clinical trial was performed on 24 patients who were admitted to the intensive care unit (ICU) from 20 March to 20 September 2007. All patients with serious injuries or with major non-abdominal surgeries were included if they met the inclusion criteria, and were assigned randomly to one of the study groups. Patients in Group 1 received intensive insulin therapy, and patients in Group 2 were treated with metformin. Moreover, the Acute Physiology And Chronic Health Evaluation (APACHE) II scoring system was used to grade disease severity.
Results: Both glycaemic management protocols led to significantly improved glucose levels without any report of hypoglycaemia. The mean initial glucose levels for the insulin group decreased significantly after the intravenous infusion of insulin ($p < 0.001$). Additionally, the blood glucose concentration was significantly lower after two weeks of metformin administration compared to baseline measurements ($p < 0.001$). Moreover, the blood glucose concentration decrease during these two weeks was significantly higher in the insulin group ($p = 0.01$). Besides, APACHE II score was lower than baseline at the end of the study for both therapeutic groups (score of 10 vs. 15 [insulin] and 16 [metformin]). Finally, new renal dysfunction (maximum serum creatinine level at least double the initial value) was observed in three of the patients (two patients from the metformin group and one from the insulin group) in the last days of the protocol, although none of the patients showed lactic acidosis after ICU admission.
Conclusions: Both metformin and intensive insulin therapy significantly decreased hyperglycaemia in ICU patients. Insulin caused a greater reduction in blood glucose concentration but required more attention and trained personnel. **(Pol J Endocrinol 2012; 63 (3): 206–211)**

Key words: *hyperglycaemia, ICU, insulin, metformin*

Streszczenie

Wstęp: Dowody naukowe wskazują, że zapobieganie hiperglikemii u osób w stanie krytycznym przy zapewnieniu odpowiedniego poboru kalorii może zmniejszyć śmiertelność i chorobowość. Celem niniejszego badania było porównanie wpływu metforminy i insuliny na występowanie hiperglikemii u pacjentów leczonych na oddziale intensywnej opieki medycznej (OIOM).
Materiał i metody: Badanie z randomizacją przeprowadzone metodą podwójnie ślepej próby obejmowało 24 chorych przyjętych na OIOM w okresie od 20 marca do 20 października 2007 roku. Wszystkich pacjentów z ciężkimi obrażeniami lub po poważnych zabiegach chirurgicznych niedotyczących jamy brzusznej, którzy spełniali kryteria włączenia, przydzielono losowo do jednej z grup terapeutycznych. U chorych przydzielonych do grupy 1. stosowano intensywną insulinoterapię, natomiast chorym z grupy 2. podawano metforminę. Do oceny ciężkości stanu chorych wykorzystano skalę APACHE (*Acute Physiologic Assessment and Chronic Health Evaluation*) II.
Wyniki: Oba protokoły leczenia hipoglikemizującego spowodowały istotną poprawę wyrównania glikemii, przy czym nie odnotowano żadnego przypadku hipoglikemii. W grupie stosującej insulinoterapię średnie stężenie glukozy obniżyło się istotnie w stosunku do wartości wyjściowych po dożylnym wlewie insuliny ($p < 0, 001$). U osób leczonych metforminą po 2 tygodniach przyjmowania leku stężenie glukozy we krwi było istotnie niższe od poziomu wyjściowego ($p < 0,001$). Redukcja stężenia glukozy w ciągu tych 2 tygodni była istotnie większa w grupie przyjmującej insulinę ($p = 0,01$). W obu grupach terapeutycznych punktacja w skali APACHE II w momencie zakończenia badania była niższa od wartości wyjściowych (10 punktów *v.* 15 [insulina] i 16 [metformina]). U 3 chorych (2 osoby przydzielone do leczenia metforminą i 1 osoba przydzielona do insulinoterapii) zaobserwowano rozwój niewydolności nerek *de novo* (maksymalne stężenie kreatyniny w surowicy co najmniej 2-krotnie większe od wartości wyjściowych) w ostatnich dniach stosowania protokołu leczenia hipoglikemizującego, chociaż u żadnego z pacjentów nie stwierdzono kwasicy mleczanowej po przyjęciu na OIOM.
Wnioski: Zarówno leczenie metforminą, jak i intensywna insulinoterapia istotne zmniejszają hiperglikemię u pacjentów na OIOM. Insulina powoduje większą redukcję stężenia glukozy, jednak jej stosowanie wymaga większej uwagi, a personel medyczny musi być odpowiednio przeszkolony. **(Endokrynol Pol 2012; 63 (3): 206–211)**

Słowa kluczowe: *hiperglikemia, OIOM, insulina, metformina*

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Introduction

Critical illness is defined as any condition in which the patient needs mechanical aid or pharmacological agents to support failing vital organ functions. Because of the emergence of intensive care medicine in recent decades, patients now can survive diseases and trauma that were previously lethal [1]. Critical illness is associated with many endocrine and metabolic disturbances, among which are changes to the carbohydrate metabolism. Because of the stress of trauma or illness, critically ill patients (CIPs) frequently present hyperglycaemia, irrespective of whether or not they were diabetic before admission [2]. Hyperglycaemia has been detected in approximately 50% of non-diabetic intensive care unit (ICU) patients with sepsis [3].

It has been suggested that hyperglycaemia during injury compensates for volume loss by promoting the movement of cellular fluid into the intravascular compartment or by liberating water bound to glycogen. Alternatively, stress hyperglycaemia may have evolved as a means of ensuring an adequate concentration of glucose in the blood to provide the energy requirements of glucose consumers such as the brain, phagocytes and reparative cells [3].

The causes of stress hyperglycaemia include the presence of excessive counter-regulatory hormones (glucagon, growth hormone, catecholamine, and glucocorticoid, either endogenous or exogenous), and high circulating or tissue levels of cytokines (in particular tumour necrosis factor-alpha [TNF alpha] and interleukin-1). These metabolic changes result in the failure of insulin to suppress hepatic gluconeogenesis despite hyperglycaemia; in addition, insulin-mediated glucose uptake into skeletal muscle is impaired [4]. Mechanisms include insulin resistance, absolute or relative insulin deficiency, impaired glucose metabolism, and the effect of medications such as corticosteroids and densely caloric entrance and parenteral nutritional supplements [5].

Several recent studies have shown that the development of hyperglycaemia is an important risk factor in terms of mortality and morbidity of critically ill patients, and also of the mortality and length of ICU and hospital stay of trauma patients. Hyperglycaemia is associated with infectious morbidity. Similarly in severely burned children, the mortality, incidence of bacteraemia and fungaemia, and the number of skin grafting procedures is higher in hyperglycaemic patients than in normoglycaemic patients [5].

Insulin remains the obvious treatment for hyperglycaemia, although evidence documenting the clinical benefit of aggressive insulin therapy in the ICU is scarce [4]. Strict control of blood glucose levels, especially maintaining it between 80 and 110 mg/dL with insulin, has reduced morbidity and mortality compared to tolerating stress hyperglycaemia as a potentially beneficial response. Several clinical complications, such as severe infections, acute renal failure and critical illness polyneuropathy have been shown to be reduced. In addition, the number of patients who developed liver dysfunction with hyperbilirubinaemia was lowered and the patients needed fewer red blood cell transfusions. Patients were also less dependent on prolonged mechanical ventilation and intensive care.

These results support the adoption of this low-cost intervention as standard care for critically ill patients [1, 6]. Both blood glucose control and the glucose-independent effects of insulin appear to contribute to the useful effects of this therapy [7].

Although several insulin protocols have been applied in different settings of CIPs [6, 8, 9], they have carried the highest risk of hypoglycaemia [10]. Intensive insulin therapy increases entry of potassium and magnesium from the extra-cellular to the intracellular space, leading to hypokalaemia and hypomagnesaemia [11, 12] which promote insulin resistance [13–15] and a higher blood glucose level (BGL). Thus, the administration of more insulin is unavoidable, thereby beginning a vicious cycle with adverse outcomes. In this regard, blood levels of potassium and magnesium as well as BGL must be closely monitored during insulin therapy [16].

Metformin has recently been suggested as an alternative means of correcting hyperglycaemia in severely injured patients [17]. By its inhibition of gluconeogenesis and augmentation of peripheral insulin sensitivity, metformin directly counters the two metabolic processes which underlie injury-induced hyperglycaemia. Metformin has also been shown to increase the rate of muscle protein synthesis in patients following severe burn injury (unpublished data) and to reduce circulating lipids without affecting insulin secretion [17]. Thus, in a way analogous to that of insulin, metformin may have efficacy in critically injured patients as both an anti-hyperglycaemic and muscle protein anabolic agent [18]. Although it has been suspected for lactic acidosis (LA) [19], several studies have demonstrated that metformin, per se, does not promote LA, and this phenomenon is coincidental with other underlying CIs [20, 21].

Except for two trials in small populations of burned patients [18, 22], the efficacy of metformin in glycaemic control in CIPs and trauma patients has not been studied. Therefore, Mojtahedzadeh et al. conducted a study in which they showed that metformin is a safe adjunct that decreases insulin requirements, and they suggested the addition of metformin to critically ill patients who have difficult titrations of blood glucose levels [23].

Moreover, one of those studies on burned patients suggested a potential clinical efficacy of metformin in reducing stress-induced hyperglycaemia by increasing

glucose clearance [22]. Another study demonstrated a significant anabolic effect on muscle protein with metformin and a modest response with insulin. Findings also suggest that metformin and insulin may work synergistically to further improve muscle protein kinetics [18].

The purpose of this study was to compare the metabolic effects of metformin and insulin on hyperglycaemia in ICU patients during the height of their hyper-metabolic response.

Methods

Patients and study protocol

This double-blind randomised clinical trial was performed on patients who were admitted to the intensive care unit (ICU) at Sina hospital in Teheran, Iran from 20 March to 20 September 2007. All patients with serious injuries and major non-abdominal surgeries were included if they were non-diabetic, had BGL more than 110 mg/dL, and were diagnosed as having Systemic Inflammatory Response Syndrome (SIRS) (Table I). Exclusion criteria were any of the following: age more than 75 years or less than 18 years, history of diabetes, abdominal injuries or surgeries, oral intolerance, severe diarrhoea or vomiting, Non Per Os (NPO), blood pressure less than 70 mm Hg, serum bicarbonate less than 13 mEq/L, blood lactate more than 4.5 mmol/L, serum creatinine (cr) level more than 1.2 mg/L, or raised liver enzymes.

Each patient was included only once in the study, even if he or she had been hospitalised more than once. A sample size of 28 was calculated for this study. These patients were divided into two groups using a simple block randomisation method in blocks of four.

Cannulation of the radial artery was done for all patients to facilitate blood sampling and to prevent frequent needle injuries. During ICU admission, patients in Group 1 received intensive insulin therapy, and patients in Group 2 were treated with metformin.

Before the start of the study, patients were fully informed of the format and consequences of the study and signed a consent form. This study was conducted following approval by the Ethics Committee of Teheran University of Medical Sciences and was in accordance with the ethical principles described in the Declaration of Helsinki.

Glycaemic management protocol and glucose measurements

In Group 1, regular insulin that was prepared with 10 units in 50 ccs 0.9% NaCl was injected in one peripheral vein using a syringe pump (SP-500, JMS, Japan). The dose of this insulin was determined based on the patient's initial blood glucose according to the data in Table II. With regard to the potential risk of hypoglycaemia, the patients' blood glucose was monitored every two hours by means of a bedside glucometer (Sapphire, Medi Smart, Switzerland). While being in the range of 80–110 mg/dL, intravenous injection of insulin was ceased for one hour and measurement was repeated after one hour and a decision was made according to the result. Moreover, in patients who needed more than 5 units/h insulin, blood glucose was monitored every one hour. To equalise the conditions in the two groups, blood glucose was also measured every six hours in the laboratory.

Patients in Group 2 received oral metformin, with a 1,000 mg dosage given at 12-hourly intervals via a nasogastric tube, or orally if possible. Their blood glucose was assessed in the laboratory every six hours. In this group, plasma lactate concentrations were determined before the administration of the next dose of metformin every 12 hours because of the potential risk of lactataemia, using ACCUT LACTATE machinery (Roche Co). If the plasma lactate level exceeded 4.5 mmol/L, or increased by more than 2 mmol compared to the previous measurement, metformin administration would be stopped, and the patient excluded from the study.

Table I. *Inclusion criteria*

Tabela I. *Kryteria włączenia do badania*

Non-abdominal injuries or surgeries
Blood glucose level more than 110 mg/dL
Diagnosis of Systemic Inflammatory Response Syndrome (SIRS)
Defined as presence of two or more of the following:
— body temperature more than 38°C or less than 36°C
— heart rate more than 90/min
— respiratory rate more than 20/min or Paco2 < 32 mm Hg
— WBC more than 12,000 or less than 4,000 or more than 10% Band cell

Table II. *Insulin treatment protocol*

Tabela II. *Protokół insulinoterapii*

Blood glucose	Insulin [unit/h]
80–110	0
111–130	1
131–150	2
151–170	3
171–190	4
191–210	5

Health evaluation

The Acute Physiology And Chronic Health Evaluation (APACHE) II scoring system [24] was used to grade disease severity. To calculate this score, arterial blood gas (ABG), electrolytes, complete blood count, and Glasgow Coma Score (GCS) level were assessed daily, and pulse rate, respiratory rate, blood pressure and body temperature was determined every two hours, for all patients in both groups.

Statistical analysis

In order to compare the mean values of quantitative variables, an independent T-test was performed. Student's paired T-test was used for comparison between pre- and post-treatment period measurements in each group. Results were expressed as mean ± SD and a p value < 0.05 was accepted as significant.

Results

Comparison between metformin group and insulin group

A total of 28 patients were included in our study, of whom 14 were assigned to each of two therapeutic groups. Two patients from the metformin group encountered severe conditions and became NPO and were excluded from the study. One of the insulin group patients died, and another one from this group chose not to undergo the study because his wounds had healed and he was ready for discharge. Data from these patients is not included in this report. Selected characteristics of patients in the insulin group and the metformin group who completed the entire two weeks of the study are set out in Table III. There were no significant differences between insulin and metformin-treated patients regarding the number of patients, age ($p = 0.62$), or sex ($p = 1$). The hospital course of the 24 remaining study subjects was uneventful during the two weeks of study, with the maintenance of good haemodynamics, urine output, and organ function.

Effect of the protocol on glycaemic control

The glycaemic management protocol led to significantly improved glucose levels ($p < 0.001$) without any report of hypoglycaemia (defined as glucose values lower than 40 mg/dL) during the treatment period. The mean (SD) and median initial glucose levels for the insulin group were 209 (35) mg/dL and 202 mg/dL, respectively. These decreased significantly to 125 (7) mg/dL and 126 mg/dL after the intravenous infusion of insulin ($p < 0.001$). Measurements of glucose kinetics are shown in Table IV.

The blood glucose concentration was significantly ($p < 0.001$) lower after two weeks of metformin administration (the mean (SD) and median of 129 (8) mg/dL and 130 mg/dL) compared to the baseline (the mean (SD) and median of 177 (22) mg/dL and 182 mg/dL) measurements. Moreover, the blood glucose concentration decrease during these two weeks was significantly higher in the insulin group ($p = 0.01$).

The distribution of glucose values for the insulin group and the metformin group is shown in Figure 1.

General condition and organ system dysfunction

The APACHE II score was lower than baseline at the end of the study for both therapeutic groups (*i.e.* scores of 15 [insulin] and 16 [metformin] *vs.* 10). New renal dysfunction after ICU admission, defined as initial serum creatinine level of 1.5 mg/dL or lower with maximum serum creatinine level of 2.5 mg/dL or higher during ICU admission or initial serum creatinine level lower than 1.5 mg/dL with maximum serum creatinine level during ICU admission at least double the initial value [6], was observed in three of the patients according to the second part of the definition. Two patients from the metformin group and one from the insulin group with initial creatinine levels of 0.5, 1, and 0.7 achieved levels of 1.2, 1, and 1.9 on days 11, 14, and 14 of the treatment period, respectively. However, they weren't excluded because their creatinine level was lower than 1.2 mg/dL or they had finished the treatment period. Additionally, none of the patients showed lactic acidosis, and GCS levels were improved significantly in both groups. Mean

Table III. *Baseline patient characteristics*

Tabela III. *Wyjściowa charakterystyka chorych*

	Insulin group	Metformin group
Age (years), mean ± SD	43.16 ± 11.67	39.91 ± 19.05
Gender (M/F)	8/4	9/3
APACHE II score (first day/last day)	15/10	16/10

Values are presented as mean ± SD; APACHE — Acute Physiology And Chronic Health Evaluation

Table IV. *Comparison of initial and final glucose values*

Tabela IV. *Porównanie początkowych i ostatnich wyników pomiarów stężenia glukozy*

	Insulin group	Metformin group
Initial blood glucose, mean (SD)	209 (35)	177 (22)
Blood glucose after 2 weeks, mean (SD)	125 (7)	129 (8)
Blood glucose decrease after 2 weeks of treatment, mean (SD)	84 (37)	47 (23)

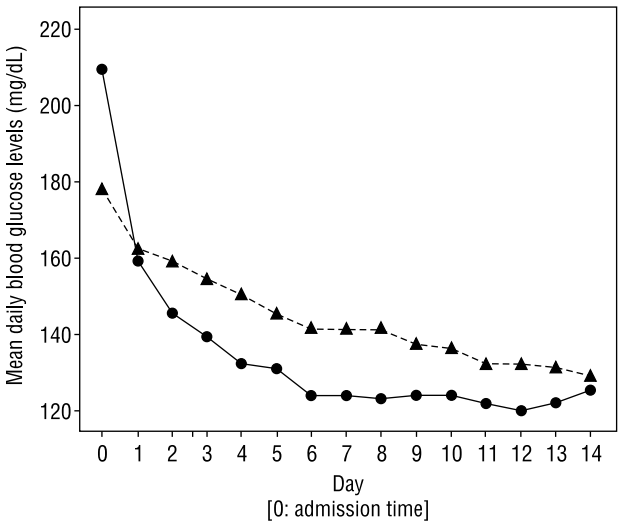

Figure 1. *Temporal trend of blood glucose levels in protocols: insulin (●) and metformin (▲) during the period of study*

Rycina 1. *Zmiany stężenia glukozy w czasie u osób leczonych insuliną (●) i metforminą (▲) w okresie badania*

increases were from 10.66 to 11.41 in the insulin group [p = 0.012], and from 10.58 to 11.41 in the metformin group [p = 0.005]).

Discussion

Glycaemic control by protocols

There have only been a few studies investigating the role of metformin in critically ill and trauma patients. As expected from previous studies [18, 22, 23], metformin did significantly decrease hyperglycaemia in ICU patients. However, our study not only failed to identify any superiority of metformin over insulin, but we also found that insulin caused a greater reduction in blood glucose concentration. Similar to our results, Gore et al. [22] found that plasma glucose concentrations were significantly lower in those subjects receiving metformin than a placebo. Additionally, in another study by Gore et al. [18], the arterial glucose concentration was significantly lower after one week of metformin administration compared to baseline measurements. In contrast to our study, the intra-arterial infusion of insulin resulted in an insignificant (8%) decrease in the arterial concentration of glucose, but during metformin treatment insulin administration into the femoral artery decreased the arterial glucose concentration by a significant 20%, which shows the synergistic effect of these two drugs on glycaemic control. Likewise, Mojtahedzadeh et al. conducted a study in which they sought to investigate the effectiveness and safety of metformin in glycaemic control in patients traumatised by critical illness by measuring the blood glucose, lactate, and pH values, in addition to the patients' insulin requirements when insulin was co-administered with metformin. They showed that metformin is a safe adjunct that decreases insulin requirement, and they suggested the addition of metformin to critically ill patients who have difficult titrations of BGLs. Additionally no significant difference in the control of glycaemia was observed between three protocols consisting of insulin (Group A), metformin (Group B) and both (Group C). This finding contradicted our result which showed a significantly higher decrease in the insulin group. Comparing initial BGL and mean weekly values showed a significant reduction in Groups A and B, but the 36% reduction in admission BGL in Group C was not statistically significant. However, adjunct therapy caused less need for insulin administration [23].

General condition

The APACHE II score was lower than baseline at the end of our research for both therapeutic groups. Likewise, work by Krinsley et al. [6] has demonstrated a median APACHE II score decrease from 16 to 15 after treatment with insulin and oral agents. Research by Mojtahedzadeh et al. also showed that the reduction in basal APACHE II score in Group B (metformin) was significant, although no significant difference was observed in weekly APACHE II score between Groups A, B, and C or within the patients.

Safety of metformin in CIPs

In our research, none of the treatment protocols led to hypoglycaemia. This result is compatible with previous work [6] in which the percentage of patients with marked hypoglycaemia was 0.35% during the baseline period and 0.34% during the treatment period. However, similar to our study, no complications such as hypoglycaemia, hypokalaemia, hypomagnesaemia, or lactic acidosis was observed in the Mojtahedzadeh et al. study [23].

Moreover, in the abovementioned study [6], metformin was shown to cause new renal dysfunction after ICU admission in three patients, and this is similar to our results.

Efficacy of metformin in acute care medicine

Gore's study [18] would suggest that even if metformin is inadequate alone to sufficiently normalise glucose concentrations in critically ill patients, its adjuvant use may increase insulin's actions for both improved glycaemic control and as an anabolic agent for muscle. Furthermore, metformin may have a clinical use in maintaining proper glycaemic control in those survivors of critical illness or injury who cannot be safely discharged from intensive care because of their continued need for in-

sulin and/or the frequent monitoring of plasma glucose that is necessary with intensive insulin therapy.

Conclusions

The findings of Mojtahedzadeh et al. [23] are the first evidence that metformin is safe in an ICU setting, and that metformin improves insulin sensitivity and requirements without causing hypoglycaemia.

Similarly, the findings of this study would suggest that intensive treatment with both insulin and metformin administration is sufficient to normalise plasma glucose concentrations in critically ill patients, although insulin works more strongly and decreases glucose concentrations by more than metformin does.

Both metformin and intensive insulin therapy significantly decreased hyperglycaemia in ICU patients. However, insulin caused a greater reduction in blood glucose concentration.

Limitations

Body mass index as an effective factor in insulin resistance had to be matched in two groups; however, we were unable to calculate this item for bedridden ICU patients.

Acknowledgement

The authors would like to thank Farzan Institute for Research and Technology for technical assistance.

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