Małgorzata Gilewska[1], Maciej Pawłowski[1], Natalia Szyłło[1], Jerzy Loba[1], Leszek Czupryniak[1, 2]
[1]Department of Internal Diseases and Diabetology, Medical University of Lodz
[2]Department of Diabetology and Internal Medicine, Medical University of Warsaw

The effect of short-term continuous intravenous insulin infusion on long-term metabolic control in patients with type 2 diabetes

ABSTRACT

Background and aims. In a large group of obese patients with type 2 diabetes achieving good metabolic control is extremely difficult, despite using all treatment options available in the outpatient setting (i.e. intensive education, intensive high-dose insulin treatment combined with oral antidiabetic agents administration). These patients may be treated with continuous intravenous insulin infusion (CIVII) in hospital as this mode of treatment improves blood glucose level rapidly and is believed to counteract glucose toxicity. However, the long-term effect of this procedure on metabolic control in diabetes is unknown. We conducted the study to assess the effect of short term CIVII on long term glucose control in obese subjects with type 2 diabetes.

Material and methods. The experimental group comprised of 36 type 2 diabetes patients treated with insulin [23 women and 13 men, mean age (± SD) 59.9 ± ± 7.7 years, diabetes duration 6.3 ± 3.0 years, body weight 92.9 ± 19.1 kg, BMI 33.5 ± 5.8 kg/m^2, HbA_{1c} 9.7 ± 1.8%]. In all subjects body weight, BMI, waist-to-hip ratio (WHR), blood pressure, fasting plasma triglycerides, total cholesterol, LDL and HDL cholesterol, and HbA_{1c} levels were measured before and 6 months after CIVII. CIVII was applied for at least 72 hours; it consisted of basal insulin infusion and three 90-min insulin boluses per day administered at the meal time. Capillary blood glucose level was measured every 90–120 min throughout the day and night. During the study period the subjects who used oral antidiabetic medication maintained it at stable doses. In the control group of 24 type 2 diabetes patients (mean age 61.3 ± ± 7.2 years, BMI 32.8 ± 5.1 kg/m^2, HbA_{1c} 9.4 ± 1.6%), who were subjects of a standard outpatient care, the same parameters as in the experimental group were examined at baseline and after 6-months.

Results. In obese type 2 patients 6 months after CIVII treatment HbA_{1c} decreased significantly to 8.8 ± 1.6% ($p < 0.05$); however, no improvement in body weight, WHR, blood pressure or plasma lipid parameters was noted. Shortly after CIVII, daily insulin dose was significantly reduced (from 64.5 ± 24.6 at baseline to 50.7 ± 10.8 IU/day on discharge from the hospital, $p < 0.05$); yet 6 months later it was similar to the baseline insulin requirement. In the control group no statistically significant changes in analysed parameters were found during the study period.

Conclusion. In patients with type 2 diabetes with poor metabolic control CIVII results in significant improvement of long-term glucose control, with no effect on other metabolic parameters. (Clin Diabet 2015; 4, 6: 221–225)

Key words: type 2 diabetes mellitus, insulin resistance, hyperglycaemia, intravenous insulin infusion

Address for correspondence:
lek. Małgorzata Gilewska
Klinika Chorób Wewnętrznych i Diabetologii
USK im. WAM — CSW
ul. Pomorska 251, 92–213 Łódź
e-mail: gosiagilewska@gmail.com
Clinical Diabetology 2015, 4, 6, 221–225
DOI: 10.5603/DK.2015.0029

Translation: lek. Małgorzata Kamińska
Received: 23.07.2015 Accepted: 08.10.2015

Introduction

Some patients with type 2 diabetes fail to achieve optimal metabolic control in the outpatient settings despite intensive insulin therapy and progressive dose escalation. Prolonged hyperglycaemia affects unfavourably insulin secretion and action (glucose toxicity) and increases insulin resistance [1]. In these patients continuous intravenous insulin infusion (CIVII) in hospital settings may be beneficial [2].

Continuous intravenous insulin infusion is a method of insulin therapy used in patients with acute diabetes complications, in life-threatening conditions and during perioperative period; however, it is not considered a routine treatment in poorly controlled type 2 diabetes. Insulin given by intravenous route has 100% bioavailability. Due to rapid onset and short time of action of insulin administered intravenously, it is possible to modify the basal rate and prandial boluses according to measured glucose values and to adjust precisely the dose of insulin. This allows for achieving rapid improvement of metabolic control. However, it has not been established whether this procedure exerts a long-term effect or reduces glycated haemoglobin (HbA_{1c}) level [3–5].

The aim of the study was to assess the effect of CIVII on long-term glycaemic control in patients with type 2 diabetes.

Material and methods

The study included 60 type 2 diabetes patients with insufficient metabolic control (HbA_{1c} > 7%), treated with insulin or insulin plus metformin, using multiple insulin injection regimen (4 or 5 injections per day) since at least 1 year. All participants were treated at the Outpatient Clinic of Diabetology, University Teaching Hospital No 1, Lodz.

The following exclusion criteria were adopted:

— newly diagnosed type 2 diabetes;
— autoimmune diabetes;
— diabetes caused by other diseases;
— diabetes decompensation caused by transient conditions (interruption of medication, injury, surgery, corticosteroid therapy);
— neoplastic disease;
— diagnosed advanced chronic diabetes complications (micro- or macroangiopathy);
— failure to obtain patient's consent for hospitalization.

The study protocol has been approved by Research Ethic Committee of Medical University of Lodz (approval number RNN 930/11/KB). All patients were informed about the details of the project and the aim of the study, and gave informed written consent for participation in the study.

Table 1. Study groups' characteristic

	Experimental group	Control group	
Number of subjects	36	24	NS
Gender (women/men)	23/13	14/10	NS
Age (years)	59.9 ± 7.7	61.3 ± 7.2	NS
Weight [kg]	92.9 ± 19.1	94.6 ± 17.2	NS
BMI [kg/m^2]	33.5 ± 5.8	32.8 ± 5.1	NS
Waist circumference [cm]	98.3 ± 12	99.7 ± 13.1	NS
Hip circumference [cm]	101.3 ± 14	105.7 ± 11.2	NS
WHR	0.92 ± 0.06	0.91 ± 0.08	NS
Diabetes duration (years)	6.3 ± 3.0	6.1 ± 4.1	NS
HbA_{1c} (%)	9.7 ± 1.8%	9.4 ± 1.6	NS

BMI — body mass index; WHR — waist-to-hip ratio
Data are presented as numbers or mean ± SD

The patients were randomized to experimental or control group. The patients from the experimental group were referred to the Department of Internal Diseases and Diabetology of Medical University of Lodz in order to perform intravenous insulin infusion. The patients from the control group continued the treatment in Outpatient Clinic of Diabetology, Teaching Hospital no 1, Lodz. Table 1 presents study groups characteristics.

Intravenous insulin infusion (for at least 72 hours) consisted of basal rate and three 90-minute prandial boluses. Short-acting human insulin was administered in 0.9% NaCl solution (50 IU in 50 mL, 1 IU/1 mL) using automatic infusion pump. Initial insulin dose was established based on insulin doses used by the patient before the study. Initial basal rate (in IU/h) was calculated as 50% of the patient's daily insulin dose divided by 24. Remaining 50% of insulin dose were divided into 3 prandial boluses (breakfast, lunch and dinner).

Capillary blood glucose level was measured every 60 min during the day and every 120 min during night-time; basal infusion rate was then modified according to study protocol:

— glucose level < 40 mg/dL — infusion rate reduction by 0.4 UI/h;
— glucose level 40–60 mg/dL — infusion rate reduction by 0.2 UI/h;
— glucose level 60–80 mg/dL — infusion rate reduction by 0.1 UI/h;
— glucose level 80–120 mg/dL — no changes in infusion rate;
— glucose level 120–150 mg/dL — infusion rate increase by 0.1 UI/h;
— glucose level 150–200 mg/dL — infusion rate increase by 0.2 UI/h;

— glucose level > 200 mg/dL — infusion rate increase by 0.3 UI/h and additionally a bolus of 60 UI/h for 4 min.

Prandial boluses lasted 90 min and were initiated at the beginning of the meal at strictly defined time during the day: 7.30–9.00, 12.00–13.30, 19.00–20.30.

Each bolus was divided into three periods: during first 20 min the patient received 30% of the dose, during subsequent 30 min — 50%, and during remaining 50 min — 20% of estimated insulin dose for one prandial bolus. Subsequent prandial boluses were established based on glucose-lowering effects of previous boluses.

Intravenous insulin infusion was continued until achieving sufficient metabolic control, but not shorter than 72 h. Sufficient metabolic control was defined as fasting and pre-prandial blood glucose within the range of 70–120 mg/dL and blood glucose 2 h after meal < 160 mg/dL.

In the control group, insulin doses were modified based on glycaemic profile including glucose measurement performed in fasting state, prior to and 2 h after main meals and at the bedtime. The patients performed self-measurements of glucose levels and noted the results in the diabetes diary. They were asked to bring the diary to follow-up visits every 3 months.

In both groups examination was performed at baseline and after 6 months of follow up and included: medical history, physical examination, anthropometric measurements, blood pressure, HbA_{1c}, and lipid profile.

In both groups necessary insulin dose modifications were made during follow-up visits performed every 3months to achieve acceptable glycaemic profile. All patients were given recommendations concerning the diet and administration and adjusting of insulin doses. Patients were recommended to modify insulin doses according to provided written instructions.

The treatment goal was to achieve glucose level within the range of 70–120 mg/dL in a fasting state and before meals and < 160 mg/dL 2 h after meals, without hypoglycaemic episodes. In patients receiving metformin the dose was constant throughout the whole study period.

Statistical analyses were performed using the Statistica 9.1. software.

Results

In the experimental group 6 months after CIVII HbA_{1c} value decreased from 9.7 ± 1.8 to 8.8 ± 1.6% ($p < 0.05$). Shortly after CIVII daily insulin requirement decreased from 64.5 ± 24,6 to 50.7 ± 10.8 IU/day ($p < 0.05$), yet 6 months later it was similar to baseline values (69.6 ± 27 IU/day vs. 64.5 ± 24.6 IU/day) (Fig. 1). No changes in body weight, waist circumference, blood pressure, or lipid profile were noticed (Tab. 2).

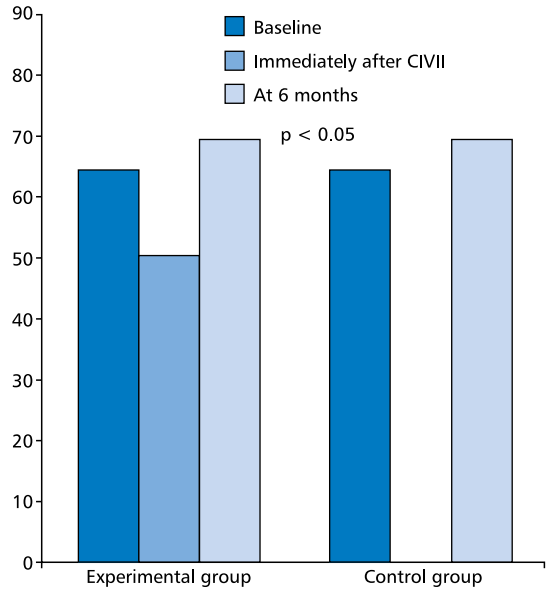

Figure 1. Changes in daily insulin dose in both groups during the study

Table 2. Analysis of assessed parameters in the experimental group

Experimental group	Baseline	At 6 months	
Weight [kg]	92.9 ± 19.1	92.7 ± 18.8	NS
BMI [kg/m^2]	33.5 ± 5.8	33.7 ± 6.4	NS
Waist circumference [cm]	98.3 ± 12	97.4 ± 13	NS
Hip circumference [cm]	101.3 ± 14	103.6 ± 11	NS
WHR	0.92 ± 0.06	0.91 ± 0.06	NS
HbA_{1c} (%)	9.7 ± 1.8	8.8 ± 1.6	$p < 0.05$
CH [mg/dL]	206.5 ± 81.2	205 ± 61.9	NS
TG [mg/dL]	335.7 ± 336.6	239.1 ± 106.3	NS
HDL [mg/dL]	42.2 ± 7.7	43.7 ± 9.7	NS
LDL [mg/dL]	119.9 ± 42.5	116 ± 48.7	NS
SBP [mm Hg]	126.8 ± 9.8	126.8 ± 9.6	NS
DBP [mm Hg]	76.4 ± 9.7	74.3 ± 8	NS

BMI — body mass index; WHR — waist-to-hip ratio; TG — triglycerides; HDL — high-density lipoprotein; LDL — low-density lipoprotein; SBP — systolic blood pressure; DBP — diastolic blood pressure

In the control group no changes were observed in analysed parameters, but there was a significant increase in daily insulin dose (from 66 ± 22.4 IU/day to 80.4 ± 24.6 IU/day) ($p < 0.05$) (Fig. 1, Tab. 3).

Discussion

Continuous intravenous insulin infusion is a method commonly used in diabetic patients in life-threatening conditions (ketoacidosis, hyperosmolar

Table 3. Analysis of assessed parameters in the control group

Control group	Baseline	At 6 months	
Weight [kg]	94.6 ± 17.2	95.1 ± 14.5	NS
BMI [kg/m^2]	32.8 ± 5.1	34.3 ± 6.9	NS
Waist circumference [cm]	99.7 ± 13.1	99.8 ± 14.3	NS
Hip circumference [cm]	105.7 ± 11.2	106.1 ± 11.8	NS
WHR	0.91 ± 0.08	0.94 ± 0.06	NS
HbA_{1c} (%)	9.4 ± 1.6	9.2 ± 1.9	NS
CH [mg/dL]	216.6 ± 65.7	212.7 ± 69.7	NS
TG [mg/dL]	345.4 ± 372	363.1 ± 327.7	NS
HDL [mg/dL]	44 ± 7.3	43.7 ± 8	NS
LDL [mg/dL]	135.3 ± 34.8	139.2 ± 34.8	NS
SBP [mm Hg]	130 ± 6.2	128 ± 7	NS
DBP [mm Hg]	73.2 ± 9.4	74 ± 8.3	NS

BMI — body mass index; WHR — waist-to-hip ratio; TG — triglycerides; HDL — high-density lipoprotein; LDL — low-density lipoprotein; SBP — systolic blood pressure; DBP — diastolic blood pressure

hyperglycaemic syndrome, myocardial infarction, or stroke) and during perioperative period [3, 4]. Rapid onset and short time of action of insulin administered intravenously make it possible to modify the dose in response to glucose level measured at specific time point. Additionally, intravenous insulin administration provides above 100% bioavailability, which enables precise estimation of real insulin requirement [4, 5].

Continuous intravenous insulin infusion is not a standard treatment aiming at reducing blood glucose in type 2 diabetes patients with insufficient metabolic control.

Boullu-Sanchis et al. compared the effects of CIVII and continuous subcutaneous insulin infusion (CSII) and showed that both methods have comparable effectiveness in terms of glucose lowering. According to the authors, more convenient method is CSII [6]. However, it should be noted that CIVII is more feasible treatment in Poland. Continuous intravenous insulin infusion results in glycaemic control improvement, enables fast and precise insulin dose adjustment, and, in consequence, reversion to lower doses necessary to achieving normoglycaemia [6]. However, long-term effect of this procedure has not been established [4, 6]. Pouwelsa et al. used CIVII in a study performed in type 2 diabetes patients with insufficient metabolic control and achieved marked reduction of insulin requirement immediately following CIVII and HbA_{1c} level reduction 6 and 12 months later. However, it should be mentioned that after termination of CIVII, continuous insulin infusion using portable insulin pump was continued for 12 months, which could have significant impact on HbA_{1c} reduction [7].

In our study, CIVII was used followed by intensive insulin therapy including 4 or 5 injections per day. In the experimental group daily insulin requirement immediately after CIVII was significantly reduced. At 6 months after discharge from the hospital HbA_{1c} value, accepted as a measure of long-term diabetes control, was decreased by 0.9% compared with baseline. Daily insulin dose at 6 months in these patients were similar to baseline value, whereas in patients who did not receive CIVII, daily insulin dose increased by 25%. Despite elevated daily insulin dose, no HbA_{1c} reduction was observed in this group of patients.

The results of the study suggest that short-term intensive insulin therapy using CIVII may result in long-term beneficial therapeutic effects without increasing insulin doses. It is also worth pointing out that despite significant increase in insulin dose in control group, HbA_{1c} reduction has not been achieved. Therefore, glucose toxicity decrease may play an important role [5, 8, 9].

Continuous glucose infusion used in the study did not influence other assessed parameters, such as blood pressure or lipid profile.

A barrier to common use of this treatment method is the need of patient hospitalization. It seems that developing of unified, effective insulin infusion protocol is needed. Polish Diabetes Association permits the use of this procedure as an attempt to reduce insulin resistance, but does not recommend any specific protocol. Many insulin dosing regimens for intravenous infusion has been published; however, it is difficult to compare their effectiveness and safety because of differences in patients' characteristics. Great majority of them considers patients in life-threatening conditions and treated in intensive care units. The appropriate protocol should define glycaemic targets and provide clear guidelines for blood glucose monitoring and insulin dose adjustment, so that they could be easily implemented by medical staff [3, 6, 10–12].

In the presented study modified protocol proposed by Boullu-Sanchisa et al. was used. The modifications necessary to perform the study included the way of establishing initial insulin infusion rate and the amount of insulin for prandial boluses which was calculated based on insulin requirement prior to the study [6].

Furthermore, there are no recommendations in the literature on how long intravenous insulin infusion should be continued in patients with poorly controlled type 2 diabetes. In a study by Boullu-Sanchis et al. using CIVII for 5 days, glycaemic control improvement was observed after 12 hours of infusion [6]. Pouwels et al., continued CIVII for as long as 31 ± 10 days [7].

In a study performed by Meyers et al., long-term improvement of insulin secretion and insulin resistance reduction were observed following 10-day CIVII [13]. In presented study attempt was made to assess the effect of short-term CIVII. The duration of CIVII was determined according to Polish Diabetes Association guidelines which recommend that in patients with marked insulin resistance attempt can be made to reduce insulin resistance by using 72–96-hour intravenous or subcutaneous insulin infusion [2]. Based on authors own experience, extended intravenous insulin treatment is not related with additional benefits, but results in prolonged hospitalization and is cumbersome for patients.

In our study diabetes education was provided to all participants, which could influence the improvement of metabolic control [7]. However, in most of clinical trials on the impact of diabetes education on glycaemic control, the improvement of metabolic control was accompanied by body weight reduction which was of crucial importance [14–16]. Hyun et al. showed that education was related to improvement in self-control, dose adjustment by the patients and lifestyle modification, but had no effect on glycaemic profile or HbA_{1c} [17]. It should be noted that metabolic control improvement observed in hospitalized patients could have been related to strict adherence to dietary recommendations. Nevertheless, BMI remained unchanged in both groups, which negates the impact of body weight reduction on the improvement of insulin sensitivity and glycaemic control in the study group.

Both groups were treated by the same therapeutic team to avoid differences in patients' management. Education and insulin dose modification were performed by the same medical team in the hospital and outpatient care settings. However, it should be remembered that in the experimental group metabolic control could have been influenced by increased motivation due to hospitalization. This issue needs further evaluation.

The use of CIVII may be related with possible local adverse reactions, such as cellulitis at the injection site or superficial vein thrombosis. However, no such adverse reactions were observed during the study, which indicates minimal risk of these complications.

Conclusions

1. In type 2 diabetes patients with insufficient metabolic control, the use of CIVII may result in long-term improvement of metabolic control with no effect on body weight or other metabolic parameters.
2. The use of CIVII enables more precise dose estimation, and allows for achieving metabolic control improvement without increasing daily insulin requirement.

Conflict of interest statement

The authors declare no conflict of interests.

REFERENCES

1. Yki-Jrvinen H. Toxicity of hyperglycaemia in type 2 diabetes. Diabetes Metab Rev 1998; 14: 45–50.
2. Zalecenia Kliniczne dotyczące postępowania u chorych na cukrzycą 2015. Stanowisko Polskiego Towarzystwa Diabetologicznego. Diabetologia Kliniczna 2015; 4 (suppl A).
3. Krzymień J. Dożylne wlewy insuliny podczas hospitalizacji. Przew Lek 2007; 4: 73–79.
4. Kelly JL. Continuous Insulin Infusion: When, Where, and How? Diabetes Spectrum 2014; 27: 218–223.
5. Możdżan M, Możdżan M, Loba J, Markuszewski L, Ruxer J. Wpływ krótkotrwałej intensywnej insulinoterapii na dobowe zapotrzebowanie na insulinę u chorych w okresie dekompensacji cukrzycy typu 2. Wiad Lek 2006; 59: 203–207.
6. Boullu-Sanchis S, Ortega F, Chabrier G, Busch MS, Uhl C, Pinget M, Jeandidier N. Efficacy of short term continuous subcutaneous insulin lispro versus continuous intravenous regular insulin in poorly controlled hospitalized type 2 diabetic patients. Diabetes Metab 2006; 32: 350–357.
7. Pouwels M-JJ, Tack CJ, Hermus AR, Lutterman J. A Treatment with intravenous insulin followed by continuous subcutaneous insulin infusion improves glycaemic control in severely resistant type 2 diabetic patients. Diabet Med 2003; 20: 76–79.
8. Ruxer J, Chromińska-Szosland D, Bukowczyk P, Cypryk K, Loba J, Torzecka W. Porównanie efektywności intensywnej insulinoterapii z wykorzystaniem dożylnej i podskórnej pompy insulinowej. Diabetologia Polska 1995; 2: 24–27.
9. Valensi P, Moura I, Le Magoarou M, Pariès J, Perret G, Attali JR. Short-term effects of continuous subcutaneous insulin infusion treatment on insulin secretion in non-insulin-dependent overweight patients with poor glycaemic control despite maximal oral anti-diabetic treatment. Diabetes Metab 1997; 23: 51–57.
10. Furnary AP. Insulin infusions for cardiac surgery patients with diabetes: a call to reason. Endocr Pract 2002; 8: 71–72.
11. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clinic Proc 2004; 79: 992–1000.
12. Markovitz LJ, Wiechmann RJ, Harris N et al. Description and evaluation of a glycemic management protocol for patients with diabetes undergoing heart surgery. Endocr Pract 2002; 8: 10–18.
13. Meyer L, Grulet H, Guerci B, Gross A, Durlach V, Leutenegger M. Short-term intensive insulin therapy in insulin-requiring diabetes: effectiveness andfactors predicting success Diabetes Metab 1997; 23: 75–79.
14. Štrajtenberger-Trbović M, Turk-Štrajtenberger V, Šekerija M. Standardized educational program in persons with type 2 diabetes on oral hypoglucemic therapy: effects on glycemic control and body mass index. Diabetologia Croatica 2011; 40: 35–40.
15. D'Eramo Melkus GA, Wylie-Rosett J, Hagan JA. Metabolic Impact of Education in NIDDM. Diabetes Care 1992; 15: 864–869.
16. Mollaoğlu M, Beyazit E. Infulence of diabetic education on patient metabolic control. Apll Nurs Res Appl 2009; 22: 183–190.
17. Hyun KS, Kim KM, Jang SH. The effects of tailored diabetes education on blood glucose control and self-care. J Korean Acad Nurs 2009; 39: 720–730.