Safety of various methods of intensive insulin therapy in hospital condition assessed by hypoglycaemic episodes detected with the use of continuous glucose monitoring system

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Abstract

Purpose: The aim of the study was to determine the safety of three intensive insulin therapy methods: multiple daily insulin injections (MDI), continuous subcutaneous insulin infusion (CSII) and continuous intravenous insulin infusion (IVII) used in poorly controlled type 2 diabetic patients in hospital condition. The safety of these intensive insulin therapy methods was measured by the assessment of number and duration of symptomatic and symptomfree hypoglycaemic events with use of Continuous Glucose Monitoring System (CGMS, Medtronic MiniMed).

Material and methods: The study comprised 90 type 2 diabetic patients treated with conventional insulin therapy based on a twice daily injections with mean glucose profile values >14 mmol/l. The patients were randomized into three groups according to the method of insulin treatment. The first group was treated with MDI, the second group with CSII and the third with IVII. The glucose monitoring with the use of CGMS lasted 48 hours and was conducted on the second and on the third day of intensive insulin therapy. Glucose level below 3.5 mmol/l were recognized as hypoglycaemic episode. Intensive insulin treatment was continued until "near normoglycaemia" (glucose levels 4.5-10.0 mmol/l) was achieved and then conventional insulin therapy was readministrated.

Results: Mean number of symptomatic hypoglycaemic events detected with CGMS was two times higher for MDI than for IVII (p=0.04) and for CSII (p=0.04). Number of symptomfree hypoglycaemic events detected with CGMS was higher for MDI than for IVII and CSII, but the differences were insignificant (NS). Mean duration of one symptomfree hypoglycaemic event detected with CGMS was longer in MDI than in CSII (p=0.02) and IVII (p=0.03). It was not observed significant differences in mean duration of one symptomatic hypoglycaemic episode between studied groups (NS).

Conclusions: The results of study suggest that CSII and IVII treatment is associated with essentially lower number of symptomatic hypoglycaemic events and shorter mean duration of one symptomfree hypoglycaemic event than MDI.

Key words: multiple daily insulin injections, continuous subcutaneous insulin infusion, continuous intravenous insulin infusion, continuous glucose monitoring system, hypoglycaemia.

Introduction

Poorly controlled type 2 diabetic patients treated with hypoglycaemic oral drugs or conventional insulin therapy often require short-term intensive insulin treatment as part of a planned attempt to improve glycaemic control. It comprises multiple daily insulin injections (MDI), continuous subcutaneous insulin infusion (CSII) and continuous intravenous insulin infusion (IVII). MDI, CSII and IVII can in the best way imitate diurnal physiological rhythm of insulin secretion as compared to other methods of insulin treatment and enable adjusting individual dosage of insulin according to patient's physical condition, his activity and meals. Side-effects of insulin treatment, including MDI, CSII and IVII are hypoglycaemic events, which are an obvious life hazard. Symptomfree hypoglycaemic episodes – not recognized by patients are particularly dangerous.

Glycaemia monitoring is an essential element of successful diabetes-treatment. The course of diabetes is characterised by fluctuation of glycaemia and it is obvious, that sporadical measurements of glycaemia with glucose meters can not assure the proper treating. It seems, that the optimal solution of this problem can be continuous glucose monitoring systems. Continuous Glucose Monitoring System (CGMS, Medtronic MiniMed) is

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Table 1. **Characteristics of subjects**

	group 1 (MDI)	group 2 (CSII)	group 3 (IVII)	p
Number of subjects	30	30	30	NS
Sex F/M	20/10	22/8	19/11	NS
Age [years] x±SD	60.1±7.2	57.4±6.6	58.9±6.4	NS
BMI [kg/m^2] x±SD	27.1±2.6	27.5±2.4	27.5±1.9	NS
Duration of diabetes [years] x±SD	6.2±2.6	5.5±2.8	5.6±3.0	NS
Duration of insulin therapy [years] x±SD	2.9±1.9	2.6±1.7	3.1±2.4	NS
Mean daily insulin dose [I.U./kg] x±SD	0.72±1.1	0.81±0.8	0.70±1.4	NS
Blood glucose profile one day before short-term intensive insulin therapy introduction [mmol/l] x±SD	13.8±3.0	13.0±3.3	14.2±1.4	NS
HbA1c [%] x±SD	8.0±2.1	7.9±1.7	7.8±1.5	NS

one of such devices. This method enables strict assessment of glucose profile. It draws the glycaemia curve according to 288 glucose measurements per 24 hours [1-6].

The aim of the study was to determine the safety of short-term intensive insulin therapy methods: MDI, CSII and IVII in poorly controlled type 2 diabetic patients. The safety was measured by the number and duration of symptomatic and symptomfree hypoglycaemic events with use of CGMS.

Material and methods

The study comprised 90 type 2 diabetic patients with daily glucose profile (mean glucose value determined on base of four measurements during one day before breakfest, dinner and supper at 8.00, 13.00, 18.30 h respectively and 90 min after supper at 20.00 h) >14 mmol/l in the last 7 days before admission to Department of Diabetology and Metabolic Diseases at Medical University of Łódź. There were clinical grounds for their admission. Including criteria were the following: age between 50-70, at least 0.5 year of insulin treatment based on a twice daily injections of insulin mix 30/70 (Humulin M3 – Eli Lilly, Mixtard M30 – Novo Nordisk, Gensulin M30 – Bioton), body mass index (BMI) 25-30 kg/m^2. Patients with advanced neuropathy, microangiopathy, and macroangiopathy, with liver diseases and other serious general illnesses, psychiatric problems, infectious diseases, tumours, alcoholism, pregnant or breast feeding women were excluded from this study as well as patients taking corticosteroids, thyroid hormones, neuroleptics and thiazyd diuretics.

The study group consisted of 61 females and 29 males with mean age 58.8+/-7.2 yrs, mean BMI 27.4+/-2.6 kg/m^2, mean diabetes history 5.8+/-3.0 yrs and mean insulin therapy periods 2.9+/-2.0 yrs. Mean daily glucose values during the first 3 days of hospitalisation before starting the study was mean 13.7+/-3.3 mmol/l.

The patients were randomized into three groups according to the method of intensive insulin therapy. The first group was treated with MDI, the second group with CSII and the third with IVII. The groups didn't differ significantly regarding: their age, BMI, HbA1c, duration of diabetes and insulin therapy, clinical course of diabetes type 2, daily profile of glycaemia during the first 3 days of hospitalisation. Detailed characteristics of the groups are presented in the *Tab. 1*.

All patients provided written informed consent. The study was approved by the Ethics Committee for Studies in Subject at the Medical University of Łódź and was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines.

During the first 3 days of hospitalisation conventional insulin therapy was maintained and insulin doses were not modified, and the patients were adviced on dieting. Every patient was applied isocaloric diet, containing 200-250 g of carbohydrates per day, divided into 3 main meals in proportion: 20%-40%-40%, which were consumed at 8.00 am, 1.00 pm, 6.30 pm respectively. Ten measurements of blood glucose with glucose meters (MediSense Precision Q.I.D, Abbott) were performed daily since the first day of hospitalisation. Glucose measurements were taken at 8.00 am, 9.30 am, 1.00 pm, 2.30 pm, 4.00 pm, 6.30 pm, 8.00 pm, 10.00 pm, 1.00 am, 5.00 am. On the base of these glucose values daily glucose profile was determined. On the fourth day of hospitalisation at 7.00 am an intensive insulin therapy was introduced. The glucose monitoring with the use of CGMS was introduced on the second day of intensive insulin therapy.

MDI was based on the application of short-term insulin analogue LysPro (Eli Lilly) 3 times a day before every main meal and NPH insulin (Eli Lilly) at 10.00 pm. Preliminary insulin dose, applied on the first day of MDI was estimated according to daily insulin dosage, that patient had needed before the hospitalisation. 70% of daily insulin dosage was applied in form of prandial boluses in appropriate ratio: 30% before breakfast, 20% before dinner and 20% before supper and the rest – 30% of daily insulin dosage was applied at 10.00 pm [7].

CSII and IVII were applied with short-term insulin analogue LysPro (Eli Lilly). CSII was applied with the use of personal subcutaneous pump (508, Medtronic MiniMed) and IVII with the use of intravenous pump (Duet standard 50, Kwapisz). Initial insulin flow was estimated according to the algorithm proposed by Ruxer J. et al. [8]. CSII and IVII comprise three ninety minutes "prandial insulin square-boluses", which are started at the beginning of breakfast, dinner and supper at 7.00 am, 1.00 pm, 7.00 pm respectively and four basic insulin infusions lasted from 8.30 am till dinner time (1.00 pm) and from 2.30 pm till supper (7.00 pm), from 8.30 pm till 1.00 am and from 1.00 am till breakfast (7.00 am). Initial insulin dosage both for basic flow and prandial boluses was established according to

***Table 2*. Comparison of daily blood glucose profile before and on the last day of short-term intensive insulin therapy**

Subjects	Mean blood glucose (mmol/l ±SD)		p
MDI	0	13.8±3.0	p < 0.001
	1	7.9±2.1	
CSII	0	13.0±3.3	p < 0.001
	1	6.6±2.2	
IVII	0	14.2±1.4	p < 0.001
	1	7.2±1.9	

0 – Daily blood glucose profile determined one day before short-term intensive insulin therapy; 1 – Daily blood glucose profile determined on the last day of short-term intensive insulin therapy

***Table 3*. Mean number of hypoglycaemic episodes detected with CGMS during 48 h observation period**

	Mean number of symptomatic hypoglycaemic episodes detected with CGMS	Mean number of symptom-free hypoglycaemic episodes detected with CGMS
	mean±SD	mean±SD
MDI	2.0±0.1	0.85±0.1
CSII	1.15±0.14	0.65±0.12
IVII	1.15±0.12	0.55±0.16
MDI vs CSII	**p=0.04**	NS
MDI vs IVII	**p=0.04**	NS
CSII vs IVII	NS	NS

the patient weight. Insulin doses were established in 24 hours advance and since the second day of CSII and IVII were based on glucose profile obtained the previous day. If hypoglycaemia happened CSII and IVII were stopped, till glucose level reached 5.5 mmol/l [8]. If there were clinical symptoms of hypoglycaemia 40% glucose solution was applied intravenously.

All the actions connected with IVII, CSII treatment, glucose measurement with the use of glucose meters and CGMS service were carried out by professional medical staff. The glucose monitoring with the use of CGMS lasted 48 hours and started on the second day of intensive insulin therapy. Glucose level below 3.5 mmol/l were recognized as hypoglycaemic episode. Intensive insulin treatment was continued until "near normoglycaemia" (glucose levels 4.5-10.0 mmol/l) was achieved, then intensive insulin treatment was discontinued and insulin treatment based on a twice daily injections of insulin mix 30/70 was applied.

Presented data are means ±SD. Characteristics of groups, duration of hypoglycaemia and number of hypoglycaemic episodes were compared between these groups using ANOVA. All reported p values <0.05 were considered statistically significant. STATISTICA was used for all analyses.

Results

It was observed, that short-term methods of intensive insulin therapy: MDI, CSII and IVII are associated with significantly reduction of glucose values in all groups (*Tab. 2*).

Table 4. Mean duration of one hypoglycaemic episode (minute) detected with CGMS during 48 h observation period

	Mean duration of one symptomatic hypoglycaemic episode detected with CGMS	Mean duration of symptom-free hypoglycaemic episode detected with CGMS
	mean±SD	mean±SD
MDI	47±13	36±17
CSII	46±16	20±18
IVII	36±11	26±14
MDI vs CSII	NS	**p=0.02**
MDI vs IVII	NS	**p=0.03**
CSII vs IVII	NS	NS

***Table 5*. Comparison of mean daily insulin dose [IU/kg] x±SD on the second and on the thirth day of intensive insulin therapy introduction between study groups**

Time points	MDI	CSII	IVII	p
2nd day	0.77±0.9	0.74±0.5	0.71±0.6	NS
3rd day	0.82±0.2	0.79±0.4	0.84±0.3	NS

Mean number of symptomatic hypoglycaemic events detected with CGMS was almost two times higher for MDI than for IVII (p=0.04) and CSII (p=0.04) (*Tab. 3*).

Mean number of symptomfree hypoglycaemic events detected with CGMS was higher for MDI than for IVII and CSII, but the differences were insignificant (NS) (*Tab. 3*).

Mean duration of one symptomfree hypoglycaemic event detected with CGMS was longer in MDI than for CSII (p=0.02) and for IVII (p=0.03) (*Tab. 4*).

There was no significant differences in mean duration of one symptomatic hypoglycaemic episode between studied groups (NS) (*Tab. 4*).

There was no significant differences in mean daily insulin dose on the second (NS) and on the third day of intensive insulin therapy between study groups (NS) (*Tab. 5*).

Mean duration for MDI therapy was 6.0±2.0 days, for CSII 5.0±3.0 days and for IVII 5.5±2.5 days (NS).

Discussion

This study determined the safety of MDI, CSII and IVII in poorly controlled type 2 diabetic patients by evaluation of number and duration of symptomatic and symptomfree hypoglycaemic events. According to analysis of glycaemia values measured with use of CGMS, it seems that the MDI is the most dangerous method of short-term intensive insulin therapy compared with CSII and IVII. The safety of MDI, CSII and IVII in poorly controlled type 2 diabetes assessed by hypoglycaemic episodes with use of CGMS has not been analyzed either. Furthermore, the duration of hypoglycaemic episodes have not been used for assessing safety of intensive insulin therapy.

It is worth to introduce pioneering study DCCT. On the base of which it was affirmed that 36% of hypoglycaemic events were

symptomless, out of which 55% happened at night. There were no differences observed in number of hypoglycaemic events between CSII and MDI in DCCT [9].

The study carried out by Bode et al. compared two long-term intensive insulin therapy methods: MDI and CSII. 225 patients were treated with MDI for 12 months and 138 serious hypoglycaemic events were observed during this period. After that time the treatment was changed into CSII. Twenty two serious hypoglycaemic events were observed in the second year of study. It was concluded, that CSII caused 6-fold less serious hypoglycaemic events than MDI [10].

In Boland's study number of hypoglycaemic events during the intensive insulin therapy: MDI and CSII were estimated. Serious hypoglycaemic events were detected twice often in MDI than in CSII [11].

According to Eichner's study, long-term CSII causes less number of serious hypoglycaemic events than MDI. Twenty two serious hypoglycaemic events in patients treated with CSII and 273 serious hypoglycaemic events in patients treated with MDI were detected during 1 study year [12].

In Bendtson's study frequency of nocturnal hypoglycaemic events in MDI and CSII type 1 diabetic patients with use of CGMS were detected. Glucose level beneath 3.5 mmol/l was recognized as hypoglycaemic event. Nocturnal hypoglycaemic events were detected in 30% of the patients treated with MDI and 44% treated with CSII. Mean duration of symptomfree episode in CSII patients was 2 hours while in MDI patients 4 hours [13].

Chase in his study measured glycaemia profile in 11 type 1 diabetic patients for 30 days with use of CGMS. Only every sixth hypoglycaemia was detected with clinical symptoms. Definitely majority of hypoglycaemic events were symptomless and only CGMS made the hypoglycaemia detection possible [14].

Pańkowska obtained similar results suggesting, that CGMS is a very important way of detection of hypoglycaemic events. Thirty three type 1 diabetic patients were enrolled into the study. Through 3 to 4 days of the study hypoglycaemic events detected with CGMS were observed in 78% of the patients and only every fourth event was detected by glucose meter [15].

Conclusions

The results strongly suggest, that:

1. CSII and IVII are more safe methods of short-term intensive insulin therapy assessed by hypoglycaemic episodes than MDI.

2. CGMS can be very useful particularly in patients with tendency for hypoglycaemic events during poorly controlled diabetes. It significantly increases the safety of treatment through full hypoglycaemic event record.

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