Cent. Eur. J. Med. • 6(5) • 2011 • 575-581
DOI: 10.2478/s11536-011-0064-7

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Central European Journal of **Medicine**

Continuous subcutaneous insulin infusion vs. multiple daily injections

Research Article

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Received 8 November 2010; Accepted 8 May 2011

Abstract: Background: Intensive insulin therapy should be proposed for most type 1 diabetic patients. It can be achieved by a continuous subcutaneous insulin infusion (CSII) or by multiple daily injections (MDI). Debate remains regarding the optimal delivery of such therapy. Aim: To compare the efficacy of glycemic control, hypoglycemia frequency, dose of insulin and weight in the type 1 diabetic patients, after switching from MDI to CSII.Methods: In this retrospective study we analyzed HbA1c, profiles of blood glucose, weight, dose of insulin and hypoglycemia, 6 months before and 6 months after the initiation of CSII, in 18 patients with type 1 diabetes mellitus. Results: Blood glucose control is considerably improved during CSII, as measured by HbA1c and mean blood glucose concentrations. Fasting blood glucose, postprandial glucose and also of glycemic variability were significantly lower. The total insulin doses during the CSII period were significantly lower. There was a small non significant increase in weight during CSII. There was a significant decrease in a number of mild hypoglycemic events, a small non significant decrease of asymptomatic hypoglycemia and a small non significant increase of nocturnal hypoglycemia.Conclusions: CSII provides significant improvement of blood glucose control with lower risk for hypoglycemia.

Keywords: *Type 1 diabetes mellitus • Intensive insulin therapy (IIT) • Continuous subcutaneous insulin infusion (CSII) • Multiple daily injections (MDI) • Insulin analogues • Blood glucose control • Hypoglycemia*

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1. Introduction

The Diabetes Control and Complications Trial (DCCT) and the U.K. Prospective Diabetes Study (UKPDS) demonstrated that microvascular complications of diabetes can be avoided or delayed if blood glucose levels are maintained as close to the normal range as possible [1,2]. Intensive insulin therapy (IIT) is the cornerstone for tight glycemic control. Therefore IIT should be proposed for most type 1 diabetic patients to prevent long-term complications.

Insulin substitution in type 1 diabetes is based on mealtime rapid-acting and basal insulin. This can be achieved by a continuous subcutaneous insulin infusion (CSII) (often just called "insulin pump therapy") or by multiple daily injections (MDI) using a combination of long-acting basal insulin and a short-acting insulin to control postprandial hyperglycemia [3]. Although the goal of near-normal glycemic control using intensive management has been widely accepted, debate has emerged regarding the optimal delivery of such therapy. It remains controversial whether these two modalities are equally effective or if one is superior to the other.

The theoretical advantage of insulin pump therapy is its ability to mimic physiological insulin release and meet physiological insulin needs in people with insulin deficiency. Short-acting insulin is infused subcutaneously from a portable pump at one or more basal rates, with boosts in the dose activated by the patient at mealtimes. The basal and bolus functions of the pump allow separate determination and adjustment of both these insulin requirements and also allow flexibility in timing and amounts of nutritional intake and physical activity, allowing for wide variations in

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lifestyle. In addition, use of short-acting insulin makes coverage of the early-morning glucose rise ("dawn phenomenon") possible and eases sick-day management [4].

Continuous subcutaneous insulin infusion was introduced in the 1970s as a way of achieving and maintaining strict control of blood glucose concentrations in people with type 1 diabetes. Overall control, as measured by mean blood glucose concentrations and percentage of glycated hemoglobin (HbA1c), is considerably improved during treatment with insulin infusion pumps compared with the nonoptimised insulin injection therapy that was prevalent in management of diabetes during that period [5]. There was a reduction in the frequency of severe hypoglycemia. It is important to recognize that all studies from that period used regular insulin.

The last decade of the 20th century was marked by the introduction of more quickly absorbed monomeric insulins. Regular (short-acting) insulin is absorbed too slowly from the subcutaneous site to control postprandial hyperglycemia, and the delayed absorption then results in late hypoglycemia. Both of these problems have been much improved, and new fast-acting insulin analogues are now used regularly as prandial insulins in MDI, and also are indicated for CSII use [6,7].

Since the end of the 20th century new long-acting insulin analogs such as glargine and detemir have entered clinical practice; these are soluble in the insulin vial rather than being suspensions, have more predictable absorption, achieve more constant blood levels, and have at least the potential for significantly improved control. Studies with these insulins prove that they are superior comparing with human basal insulin in MDI in the term of efficacy (blood glucose regulation) and safety (less hypoglycemia and weight gain) [8,9]. Therefore, in the last decade, research is focused on comparison of CSII and MDI with insulin analogues and these two therapeutic regimens are mostly equal in the terms of efficacy and safety [10,11].

As a result of an enormous technologic advancement in blood glucose testing devices and insulin pump systems, popularity and interest for pump therapy has gained momentum in the whole world, and also in our country. During the last couple of years number of pump users started to grow.

However, the ideal insulin regimen should simultaneously achieve 2 goals: maintenance of near-euglycemia and avoidance of frequent and severe hypoglycemia and significant weight gain. The aim of the present work was to compare the efficacy of glycemic control, hypoglycemia frequency and severity, daily dose of insulin and body weight in the type 1 diabetic patients, when they switch from MDI with insulin analogues to CSII.

2. Subjects and Methods

This retrospective study included 18 patients with type 1 diabetes mellitus who started insulin pump therapy at the Clinic for Endocrinology, Diabetes and Diseases of Metabolism, Clinical Center Niš, since 2007 till the end of 2009.

Before the initiation of the CSII all of the patients were on MDI with four daily doses of insulin. All the patients received three boluses of short-acting insulin analogue Insulin aspart (NovoRapid, NovoNordisk, Denmark) before the main meals and the bedtime dose of long-acting insulin analogue; Insulin glargine (Lantus, Sanofi-Aventis, France) in 14 patients and Insulin detemir (Levemir, NovoNordisk, Denmark) in 4 patients. This therapy lasted more than a year in all of the patients. Initiation of insulin pump therapy was made according to the state regulations, meaning that patients had previously poor blood glucose control during 6 months. Patients needed to have three measurements of HbA1c during last 6 months with values over 7% and log of blood glucose self control measurements, showing poor regulation.

A programmable external pump (MiniMed Paradigm 712; Medtronic, USA) was placed and CSII was delivered with using Insulin aspart (NovoRapid, NovoNordisk, Denmark). The insulin dosage was determined by decreasing the average total insulin dosage per day over the preceding 2 weeks by 20%; 50% was given as a basal rate and 50% was used for bolus dosing, and afterward the insulin dose was corrected (both basal and boluses). All the patients were started on 1 basal rate, and correction doses were calculated for each patient on the basis of the 1700 rule, as previously described and recommended [12]. Insulin dose titration was to the next target range for glycemia: FPG and other preprandial blood glucose 5.0-7.0 mmol/l, 2h postprandial blood glucose 6.0-9.0 mmol/l, bedtime blood glucose 6.0-8.0 mmol/l and 03:00h blood glucose 5.0-8.0 mmol/l.

All insulin-dose changes were made initially at our diabetes clinic (patients were hospitalized for 10 to 14 days). After that all patients had daily telephone contact with a diabetes nurse educator for the first two to three weeks, followed by weekly telephone contacts for at least 3 months. Patients were instructed and followed by the same physician and diabetic educational nurse. As part of the routine clinic procedure, the team was available 24 hours a day for patient calls. All patients received repeated diabetes education at the start of a new treatment. Our diabetes nurse educator provided extensive education on the principle of CSII before initiation of insulin pump therapy. Patients were taught carbohydrate counting and were taught how to vary in-

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sulin doses based on varied food intake and planned exercise.

All the data were gathered as a part of the routine clinical work up and informed consent was obtained from all patients for all the procedures, and to allow use of data for research purposes.

For each subject, the following data were collected as part of their routine clinical care: age, sex, diabetes duration, weight, height, body mass index (BMI) and HbA1c.

Height and weight were measured with the subject standing. Weight was measured while they were minimally clothed without shoes, using digital scales and recorded to the nearest 100 g. Height was measured in a standing position without shoes, using a standard wall-mounted anthropometer. BMI was calculated as weight in kilograms divided by height in meters squared.

Blood glucose control was evaluated through analysis of three values of HbA1c before (measurements were taken 6 months, 3 months and just before the start of CSII) and three values of HbA1c after the initiation of CSII (measurements were taken 2 months, 4 months and 6 months after the start of CSII, which is more often than usual routine work up at every three months, but we monitored this group of patients more intensively) and analysis of three daily profiles of blood glucose (BG) in the last month before and three daily profiles of blood glucose after the initiation of CSII (in the 6th month of therapy). Analysis of HbA1C was performed at the Central Laboratory of the Clinical Center Niš (standard immunochemistry method on Olympus AU 400 analyzer at the accredited university hospital laboratory in Niš) on the day of blood collection. During the study period, patients were instructed to perform frequent blood glucose monitoring (using a calibrated memory glucose meter; Accu-Chek Active, Roche Diagnostics, Germany), usually 3 to 5 measurements daily and at least once weekly to perform daily profiles of blood glucose that included fasting blood glucose (FBG), before each meal, 2 hours postprandial, bedtime, 03:00h and FBG on the next morning (9 measurements profile). We had no possibility to use any continuous blood glucose monitoring system. We analyzed separately preprandial glycemia, postprandial glycemia, night glycemia (03:00h), mean blood glucose (MBG) and daily blood glucose variability. Hypoglycemia was recorded in, and extracted from patients' diaries. Nonsevere hypoglycemia was defined as symptoms consistent with hypoglycemia, that were relieved by the ingestion of glucose or food, not requiring the assistance of another person and confirmed by blood glucose of less than 3.9 mmol/l; asymptomatic hypoglycemia was defined as measured blood glucose of less than 3.9 mmol/l without symptoms consistent with hypoglycemia; severe hypoglycemia was defined as any hypoglycemic event requiring assistance from another person or resulting in seizure or coma and any blood glucose of less than 2.0 mmol/l; nocturnal hypoglycemia was defined as between bedtime and rising (from around 23:00h till 07:00h).

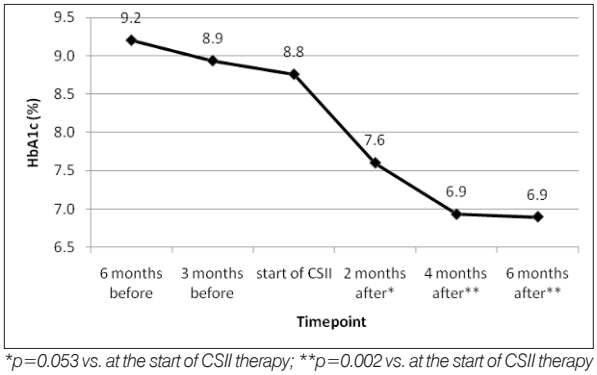
Continuous data are presented as mean ± standard deviation (SD) and categorical data are presented as numbers and/or percentages. The chi-square test was used for the comparison of categorical variables. Student's t-test was used for the comparison of continuous variables. $P<0.05$ was considered as statistically significant.

3. Results

Of the 18 type 1 diabetic patients there were 12 women and 6 men. Average age of the subjects at the beginning of the insulin pump therapy was 30.94 ± 6.35 years (from 23 to 49 years) and average duration of DM was 11.61 ± 7.64 years (from 3 to 26 years). Comparison of blood glucose control, insulin dose, body weight, BMI, and hypoglycemic events by the two insulin regimens is shown in the Table 1.

HbA1c levels during six months of MDI therapy and during six months of CSII are shown in Figure 1. There was small but no significant decline in HbA1c levels during six months of MDI therapy, before initiation of CSII (measurements were taken 6 months, 3 months and just before the start of CSII). Therefore, the HbA1c levels at the start of CSII therapy were used in the analysis. The mean HbA1c level fell after 2 months of CSII (p=0.053, ns), and continued to fall and after 4 and 6 month was significantly lower during CSII therapy than before initiation of CSII therapy (p=0.002).

Nine-point blood glucose profiles with MDI and CSII are shown in Figure 2. Mean blood glucose decreased



**p=0.053 vs. at the start of CSII therapy; **p=0.002 vs. at the start of CSII therapy*

Figure 1. Data are the change in HbA1C (%) over the course of 6 months with MDI therapy, before the initiation of the CSII, and during first 6 months with CSII therapy in the population with type 1 diabetes.

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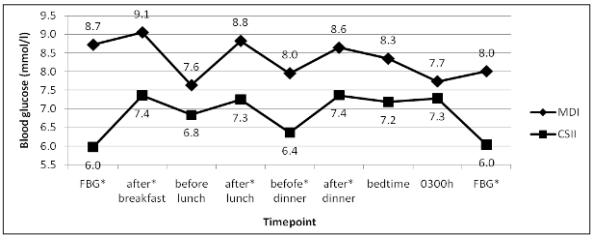
Table 1. Blood glucose control, insulin dose, body weight, BMI, and hypoglycemic events by the two insulin regimens.

	MDI regimen, before the initiation of the CSII therapy	CSII regimen, 6 months after the initiation of the CSII therapy	p
HbA1c (%)	8.8 ± 2.1	6.9 ± 1.1	0.00201
Mean BG (mmol/l)	8.3 ± 1.9	6.9 ± 1.3	0.00013
Mean SD of BG values (mmol/l)	1.9 ± 0.8	1.5 ± 0.5	0.0044
Total insulin dose (U/day)	57.33 ± 16.86	48.47 ± 12.41	0.0812
Total insulin dose (U/kg/day)	0.86 ± 0.23	0.71 ± 0.18	0.0424
Body weight (kg)	67.33 ± 11.98	68.83 ± 10.25	0.689
BMI (kg/m^2)	22.2 ± 2.9	22.8 ± 2.3	0.547
Mild hypoglycemic events (events per patient in 6 months)	68.2 ± 55.2	37.2 ± 29.3	0.0127
Asymptomatic hypoglycemic events (events per patient in 6 months)	4.3 ± 4.7	3.2 ± 3.4	0.349
Nocturnal hypoglycemic events (events per patient in 6 months)	2.4 ± 3.0	3.1 ± 3.9	0.488
Severe hypoglycemic events (total number of events in 6 months)	2	1	/

Data are means ± SD. HbA1c, body weight and the insulin doses were measured at the end of each period of treatment. Mean BG and SD of BG values from measurements of three daily profiles of blood glucose in the last month before and three daily profiles of blood glucose in the 6th month after the initiation of CSII therapy (9 measurements profile).
CSII: continuous subcutaneous insulin infusion; MDI: multiple daily injections; HbA1c: glycated hemoglobin A1c; BMI: body mass index; BG: blood glucose



CSII: continuous subcutaneous insulin infusion; MDI: multiple daily injections; FBG: fasting blood glucose
*p<0.05 MDI vs. CSII therapy

Figure 2. Data are the mean of three nine-point blood glucose profiles from the last month with MDI therapy, before the initiation of the CSII, and during the 6th month with CSII therapy in the population with type 1 diabetes.

significantly after initiation of CSII therapy. Fasting BG levels improved significantly as well as all postprandial BG levels. There was significantly lower preprandial BG level before the dinner but not before the lunch. BG levels at bedtime and at 03:00h were also lower but with no statistically significant differences. BG stability was better during CSII therapy than before initiation of CSII therapy with MDI, as assessed by the difference in the mean SD of BG values in profiles.

The total insulin doses required to maintain glucose control during the MDI treatment period were higher than those during the CSII period (CSII 48.47 ± 12.41 U/day vs. MDI 57.33 ± 16.86 U/day, p=0.08, ns, or CSII 0.71 ± 0.18 U/kg/day vs. MDI 0.86 ± 0.23 U/kg/day, p=0.04).

There was a small non significant increase in body weight during 6 months of CSII from 67.33 ± 11.98 kg to 68.83 ± 10.25 kg, or BMI from 22.2 ± 2.9 kg/m^2 to 22.8 ± 2.3 kg/m^2.

There was a significant decrease in a number of mild hypoglycemic events from 68.2 ± 55.2 (events per patient in 6 months before initiation of CSII) to 37.2 ± 29.3 (events per patient in the first 6 months of CSII), p=0.013. There was a small non significant decrease of asymptomatic hypoglycemia from 4.3 ± 4.7 to 3.2 ± 3.4 events per patient. There was a small non significant increase of nocturnal hypoglycemia from 2.4 ± 3.0 to 3.1 ± 3.9 events per patient. Severe hypoglycemic episodes were reported 3 times during the study, 2 times with MDI and 1 time during CSII (nocturnal hypoglycemia).

4. Discussion

Data regarding the improvement of overall blood glucose control in type 1 diabetic patients, as measured by mean blood glucose concentrations and percentage of HbA1c, after the introduction of CSII are numerous. Since the beginning of insulin pump therapy CSII was compared with MDI with human regular insulin. Most of the papers indicated advantages of CSII in efficacy but also in safety, with lowering the risk for hypoglycemia, less weight gain and lower total daily doses of in-

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sulin [5]. Advance in insulin therapy was both in CSII (came through technical improvements of pumps) and also in MDI, with use of insulin analogues. Data comparing therapy with rapid-acting insulin analogues against human insulin, both in CSII and MDI, show significant advantages of analogues [6,7,13]. Finally, in the last decade, research is focused on comparison of CSII (with rapid-acting insulin analogues as the gold standard) and MDI with meal boluses of rapid-acting insulin analogues and basal insulinisation with long-acting insulin analogues. Data on the safety and efficacy of this two therapeutic regimens show that they are equal [10,11] or are mildly in favor of CSII, especially in certain groups of patients [14,15]. Some head-to-head comparisons of CSII with MDI based on glargine indicate lower HbA1C or glucose levels on CSII. It can be concluded that long-acting insulin analogs have not yet replaced the need for insulin pump therapy in type 1 diabetes, and CSII is the best current therapeutic option for some type 1 diabetic subjects. The major obstacle for a wide and routine use of CSII is still high extra cost of pump and supplies and trained personnel needed to supervise the therapy (almost four times higher costs of CSII therapy comparing with MDI), although recent cost-benefit analyses have concluded that CSII is fully cost-effective when the improved quality of control and its likely effect on reducing the risk of tissue complications are taken into account [10,15].

The relative benefit of CSII over MDI was found to increase with higher baseline HbA1c, or the patients with initially worst blood glucose control had the most significant improvements in glycemic control [16-20].

Our results showing significant improvement in blood glucose control correlate with previous, considering the fact that all of our patients started insulin pump therapy according to current regulations, with previously poor blood glucose control. Overall control is considerably improved during treatment with insulin pump, as measured by HbA1c and mean blood glucose concentrations. We recorded significant lowering of fasting blood glucose, postprandial glucose and also of glycemic variability, the fact that is often emphasized as a most significant advantage of CSII [5,10,13]. Significant improvement in blood glucose control could be explained, apart from initially higher HbA1c, with very high motivation and repeated education of patients at the start of a new treatment.

Lowering of blood glucose variability, that we recorded, is one of the most important advantages of CSII, and leads to decrease of total hypoglycemic episodes per month significantly. This result correlates with most of the reported data [13,16,18,20]. There were no differences in a number of nocturnal and asymptomatic hypoglycemia, and there were few severe hypoglycemias, both with MDI and CSII, to be analyzed.

Total daily dose of insulin is lower in CSII comparing to MDI in almost all the reports [5,19,21]. Our results correlate with this data, even though difference in insulin dose is not as big as described in studies which are randomized and compare two groups of patients on CSII or MDI [13,14,22]. That is probably because our patients had poor blood glucose control at the start, and they needed more correction of the therapy after the start of CSII, leading to increase of total daily dose.

The most common metabolic adverse effect of improved glycemic control is weight gain. Intensive treatment of type 1 diabetes results in greater weight gain than conventional treatment. Participants in the DCCT who used intensive management gained about 4.5 kg more than the conventional treatment group, although there was no difference in the weight gained between patients using CSII and those using MDI [1,23]. New studies emphasize less weight gain with CSII compared to MDI; few even reported a decrease in weight [18,22]. In our patients there was small non significant increase in body weight. Weight gain was probably inevitable since our patients had such a significant improvement of blood glucose control. Follow up of these patients in the future could possibly show weight benefits of CSII that was not recorded during the first 6 months of therapy. In this group of patients on CSII we didn't perform cost-effectiveness analysis.

5. Conclusions

With all the results of continuous subcutaneous insulin infusion reported with our patients in mind, it can be concluded that this therapy provides significant improvement of blood glucose control with better safety (lower risk for hypoglycemia). Carefully selected and highly motivated type 1 diabetic patients could benefit the most. Our results show that well trained team of health professionals could perform good selection and education of patients and provide continuous subcutaneous insulin infusion as the best current therapeutic option for some type 1 diabetic subjects in our community.

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