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ORIGINAL ARTICLE

Continuous Intraperitoneal Insulin Infusion Versus Subcutaneous Insulin Therapy in the Treatment of Type 1 Diabetes: Effects on Glycemic Variability

Peter R. van Dijk, MD, PhD,¹ Klaas H. Groenier, PhD,^{1,2} J. Hans DeVries, MD, PhD,³ Reinold O.B. Gans, MD, PhD,⁴ Nanno Kleefstra, MD, PhD,^{1,4,5} Henk J.G. Bilo, MD, PhD, FRCP,^{1,4,6} and Susan J.J. Logtenberg, MD, PhD^{1,4}

Abstract

Introduction: As continuous intraperitoneal insulin infusion (CIPII) results in a more physiologic action of insulin than subcutaneous (SC) insulin administration, we hypothesized that CIPII would result in less glycemic variability (GV) than SC insulin therapy among type 1 diabetes mellitus (T1DM) patients.

Materials and Methods: Data from 5-day blind continuous glucose monitoring (CGM) measurements performed during a 26-week, prospective, observational case-control study were analyzed. The coefficient of variation (CV) was the primary measure of GV. In addition, the SD of the mean glucose level, mean of daily differences, and mean amplitude of glycemic excursions were calculated.

Results: In total, 176 patients (36% male; mean age, 49 [SD 13] years; median diabetes duration, 24 [interquartile range, 17, 35] years; glycated hemoglobin level, 63 [10] mmol/mol), of which 37 used CIPII and 139 SC insulin therapy, were analyzed. CGM data were available for 169 patients at baseline (CIPII, $n=35$; SC, $n=134$) and for 164 patients at 26 weeks (CIPII, $n=35$; SC, $n=129$). After adjustment for baseline differences, the CV was 4.9% (95% confidence interval, 1.0, 8.8) lower with CIPII- compared with SC-treated patients, irrespective of the use of multiple daily injections or continuous SC insulin infusion. There were no differences in other indices of GV between groups.

Conclusions: Despite higher blood glucose, the CV was slightly lower with CIPII compared with SC insulin therapy in T1DM patients, and other measures of GV were identical. Future studies are needed to confirm these findings and investigate whether this results in prevention of hypoglycemia and even perhaps (less) microvascular complications.

Background

CONTINUOUS INTRAPERITONEAL (IP) INSULIN infusion (CIPII) using an implantable pump is a last-resort treatment option for selected patients with type 1 diabetes mellitus (T1DM) who fail to achieve glycemic control with intensive subcutaneous (SC) insulin therapy and subsequently experience high glycated hemoglobin (HbA1c) concentrations or blood glucose variability.¹

Insulin administered by the IP route is almost entirely absorbed in the portal system, resulting in higher insulin concentrations in the portal vein catchment area, higher hepatic uptake of insulin, lower peripheral plasma insulin concentrations, and thus a mode of insulin administration mimicking the normal physiology, in contrast to SC insulin administration.^{2–7} Previous randomized studies have demonstrated favorable effects of CIPII versus SC insulin therapy on HbA1c concentrations among T1DM patients.^{8–11} However, the effects of

¹Diabetes Centre and ⁶Department of Internal Medicine, Isala, Zwolle, The Netherlands.

Departments of ²General Practice and ⁴Internal Medicine, University Medical Center Groningen and University of Groningen, Groningen, The Netherlands.

³Department of Endocrinology, Academic Medical Centre, Amsterdam, The Netherlands.

⁵Langerhans Medical Research Group, Zwolle, The Netherlands.

The study protocol was registered prior to the start of the study at the appropriate local and international registers (at ClinicalTrials.gov with clinical trial registration number NCT01621308 and at https://www.toetsingonline.nl/to/ccmo_search.nsf/fABRpop?readform&unids=C1257BA2002CC066C1257B8700360932 with clinical trial registration number NL41037.075.12).

CIPII on glycemic variability (GV), another facet of glycemic control and suggested to help predict hypoglycemia and diabetes-related complications, are relatively unknown.^{12,13}

The only three previous studies that assessed GV among CIPII-treated T1DM subjects demonstrated less GV, expressed as the SD of the mean capillary glucose level from blood glucose self-measurement, during CIPII therapy compared with SC therapy.^{9–11} However, the mean capillary glucose level was also lower during CIPII, the number of participants in these studies was small ($n = 10–24$), and most of these studies were performed before the era of rapid-acting insulin analogs and continuous glucose monitoring (CGM) measurement systems.

In order to test the hypothesis that CIPII would result in less GV than SC insulin therapy in T1DM patients, we studied the effects of CIPII on GV compared with SC insulin therapy in a large group of T1DM patients, all using rapid-acting insulin analogs.

Materials and Methods

Study design

This investigator-initiated study had a prospective, observational, matched case-control design. Inclusion took place at the Isala (Zwolle, The Netherlands) and Diaconessenhuis Hospital (Meppel, The Netherlands). The primary aim of the original study was to compare the effects of CIPII with those of SC insulin therapy, with respect to glycemic control. As a secondary outcome, and presented in this article, GV was assessed.

Patient selection

Cases were subjects on CIPII therapy who had used an implanted insulin pump (MIP 2007D; Medtronic/Minimed, Northridge, CA) for the past 4 years without interruptions of >30 days, in order to avoid effects related to initiating therapy. Inclusion criteria for cases were identical to those of a prior study in our center and have been described in detail previously.⁸ In brief, patients with T1DM, 18–70 years of age with a HbA1c level of $\geq 7.5\%$ (58 mmol/mol) and/or five or more incidents of hypoglycemic glucose (< 4.0 mmol/L) per week, were eligible.

The control group of the present study was age and gender matched to the cases and consisted of T1DM patients with SC insulin as mode of insulin administration (both multiple daily injections [MDI] and continuous SC insulin infusion [CSII]) for the past 4 years without interruptions of >30 days and an HbA1c level at time of matching of $\geq 7.0\%$ (53 mmol/mol). The ratio of participants on the different therapies (CIPII:MDI:CSII) was 1:2:2. Exclusion criteria for both cases and controls included impaired renal function, cardiac problems, and current use of oral corticosteroids.

Study protocol

There were four study visits. During the first visit, baseline characteristics were collected using a standardized case record form, and a blinded CGM measurement device was inserted for a period of 6 days. During the second visit (5–7 days later), the CGM device was removed, and laboratory measurements were performed. During the third visit, 26 weeks after visit 1, clinical parameters were collected, and

again a CGM device was inserted for a period of 6 days. During the fourth visit, 5–7 days after the third visit, laboratory measurements were performed, and the CGM device was removed. During the study period all patients received usual care.

Outcome measurements

The 24-h interstitial glucose profiles were recorded using a blinded CGM device (iPro[®]2; Medtronic). The CGM device was inserted in the periumbilical area, and in pump users it was contralateral to the (implanted) insulin pump. Patients injecting insulin were asked not to inject insulin on the same side of the sensor insertion side. Patients were instructed to perform a minimum of four blood glucose self-measurements daily during the CGM period, using a blood glucose meter (Contour[®] XT; Bayer, Leverkusen, Germany) to calibrate the sensor. All procedures related to the CGM were performed by a single trained physician (P.R.V.D.).

To account for the higher mean glucose level expected in CIPII-treated patients, as CIPII therapy is used as a last-resort treatment and CIPII-treated patients are more complex than SC-treated patients, the coefficient of variation (CV), which measures intraday variation of glucose patterns and is defined as the SD divided by the mean of blood glucose values, was chosen as the primary outcome measure of GV.^{14–17} As secondary outcomes, additional measures of GV were used.

First, as a measure of intraday GV, the mean amplitude of glucose excursions (MAGE) was defined as the mean of absolute differences between glycemic oscillation (peak and nadirs exceeding 1 SD) and calculated using the following formula:

$$MAGE \text{ (mg/dL)} = \frac{1}{k} \sum_{i=1}^k \Delta_i |_{\Delta_i > SD}$$

where k is the number of differences peak–nadir (or nadir–peak) larger than the SDs of blood glucose values. If the first difference (peak–nadir or nadir–peak) larger than the SD is a peak–nadir difference, then $\Delta_i = |\text{peak}_i - \text{nadir}_i|$. Otherwise, if the first difference larger than the SD is a nadir–peak difference, then $\Delta_i = |\text{nadir}_i - \text{peak}_i|$.

As a measure of interday variation, the mean of the daily differences (MODD), defined as the mean of absolute values of differences between glucose values taken in two consecutive days, was chosen.¹⁸ The MODD was calculated using the following formula:

$$MODD \text{ (mg/dL)} = \frac{1}{k(d-1)} \sum_{i=2}^d \sum_{j=1}^k |BG_{i,j} - BG_{(i-1),j}|$$

where $BG_{i,j}$ is the individual blood glucose values of the actual day, $BG_{(i-1),j}$ is the individual blood glucose values at the same time of the previous day, d is day, and k is the number of blood glucose values for the actual day.

In order to make comparisons with previous literature, the mean glucose level with SD was used. In addition, comparisons between CIPII and patients using MDI and CSII were made, and data from self-measurements of blood glucose (SMBG) were analyzed.

TABLE 1. BASELINE CHARACTERISTICS

Characteristic	All (n = 176)	CIPII (n = 37)	SC (n = 139)	MDI (n = 65)	CSII (n = 74)
Male sex (%)	64 (36)	13 (35)	51 (36)	21 (32)	30 (41)
Age (years)	49 (13)	49 (12)	50 (13)	52 (13)	48 (12)
Current smokers (%)	75 (43)	20 (54)	55 (40)	25 (39)	30 (41)
BMI (kg/m ²)	26 (5)	26 (4)	27 (5)	27 (5)	26 (4)
Diabetes duration (years)	24 [17, 35]	27 [22, 37]	23 [17, 35]	22 [13, 34] ^a	25 [17, 35]
Complication present (%)					
Microvascular	87 (47)	23 (62)	60 (43) ^a	27 (42)	33 (45)
Macrovascular	25 (14)	6 (16)	19 (14)	10 (15)	9 (12)
Total daily insulin dose (IU/24 h)	46 [36, 64]	55 [43, 74]	45 [35, 62] ^a	48 [38, 66]	42 [33, 60] ^a
HbA1c (mmol/mol)	63 (10)	67 (14)	62 (9) ^a	61 (8) ^a	63 (9)
Hypoglycemia					
Grade 1 ^b	1 [0, 4]	2 [0, 4]	1 [0, 4]	0 [0, 3]	2 [0, 5]
Grade 2 ^c	2 [0, 4]	1 [0, 3]	2 [1, 4] ^a	1 [0, 3]	3 [1, 5] ^a

Data are presented as *n* (%), mean (SD), or median [interquartile range] as indicated.

P values are based on appropriate parametric and nonparametric tests: ^a*P* < 0.05 compared with continuous intraperitoneal insulin infusion (CIPII).

^bDefined as the number of self-reported hypoglycemic events <4 mmol/L during the last 14 days.

^cDefined as the number of self-reported hypoglycemic events <3.5 mmol/L during the last 14 days.

BMI, body mass index; CSII, continuous subcutaneous insulin infusion; HbA1c, glycated hemoglobin; MDI, multiple daily injections; SC, subcutaneous.

Statistical analysis

Results were expressed as mean (with SD) or median (with interquartile range) for normally distributed and non-normally distributed data, respectively. A significance level of 5% (two-sided) was used. Normality was examined with *Q-Q* plots. A regression model based on covariate analysis was applied in order to take possible baseline imbalance into account. In the model the fixed factors CIPII and SC insulin therapy were used as determinants. The difference in scores was determined based on the β coefficient of the particular (CIPII or SC) group. Significance of the β coefficient was investigated with the Wald test based on *P* < 0.05. The quantity of the β coefficient, with a 95% confidence interval (CI), gives the difference between both treatment modalities over the study period adjusted for baseline differences. Statistical analyses were performed using SPSS software (IBM SPSS Statistics for Windows, version 20.0; IBM Corp., Armonk, NY). CGM data were processed using the GV calculation tool (GlyVarT; Medtronic).

The study protocol was approved by the local medical ethics committee, and all patients gave informed consent.

Results

Patients

From December 2012 through August 2013, in total, 335 patients were screened and received information about the study; 190 agreed to participate. After baseline laboratory measurements, six patients were excluded because of C-peptide concentrations exceeding 0.2 nmol/L (*n* = 4) or an enhanced glomerular filtration rate of <40 mL/min (*n* = 2). Consequently, 184 patients were followed up during the 26-week study period. Seven patients refused to wear the CGM device, and one patient withdrew informed consent because of lack of interest after the first visit. Therefore, 176 patients were analyzed, of whom 37 used CIPII and 139 used SC insulin infusion (65 MDI and 74 CSII).

Main baseline characteristics of these patients are presented in Table 1. Patients treated with CIPII were more often known with a microvascular complication, used more units of insulin per day, and had a higher HbA1c level and a higher number of self-reported hypoglycemic events. CGM data were available for 169 (CIPII, *n* = 35; SC, *n* = 134) and 164 (CIPII, *n* = 35; SC, *n* = 129) patients at baseline and final measurement, respectively. The mean interval that patients wore the CGM device was 5 (SD 1) days.

Primary outcome: CV

Over time, there was no significant change of the CV within groups (Table 2). After adjustment for baseline differences, the CV of CGM was 4.9% (95% CI, 1.0, 8.8) higher among patients treated with SC insulin therapy compared with patients treated with CIPII. After additional adjustment for differences in baseline HbA1c, number of hypoglycemic episodes, and total daily insulin dose, the CV was 4.7% (95% CI, 0.5, 8.8) higher among patients treated with SC insulin therapy compared with patients treated with CIPII.

Secondary outcome: other indices of GV

After adjustment for baseline differences, the mean glucose level during CGM was -0.9 mmol/L (95% CI, -1.6, -0.1) lower among patients using SC insulin therapy compared with CIPII-treated patients (Table 2). Although the MODD increased over time by 0.5 mmol/L (95% CI 0.01, 1.0) among CIPII-treated patients, there were no significant differences in the SD, MAGE, and MODD between the SC and CIPII treatment groups.

Secondary outcome: subgroup analysis and data from SMBG

Subgroup analysis demonstrate that patients using MDI and CSII had a lower mean glucose level (-0.9 mmol/L [95% CI, -1.7, -0.1] and -0.9 mmol/L [95% CI, -1.6, -0.1],

TABLE 2. OUTCOMES OF GLYCEMIC VARIABILITY DURING BASELINE AND LAST VISIT AND CHANGES BETWEEN THE CONTINUOUS INTRAPERITONEAL INSULIN INFUSION AND SUBCUTANEOUS INSULIN THERAPY GROUPS

	CIPII			SC			Difference between SC versus CIPII (baseline adjusted)
	Baseline	End	Change within group	Baseline	End	Change within group	
SMBG							
Mean glucose (mmol/L)	10.1 (3.1)	10.5 (2.5)	0.2 (−0.6, 1.0)	9.4 (2.0)	9.3 (1.9)	0.1 (−0.2, 0.4)	−0.6 (−1.3, 0.03)
SD (mmol/L)	4.5 (1.7)	4.1 (1.3)	−0.3 (−1.0, 0.2)	4.2 (1.1)	4.3 (1.4)	0.2 (−0.1, 0.4)	0.3 (−0.2, 0.8)
CV (%)	43.2 (10.1)	40.0 (11.0)	−2.7 (−7.4, 1.9)	43.2 (10.1)	46.1 (11.4)	1.2 (−1.2, 3.5)	5.6 (1.2, 9.9) ^a
CGM							
Mean glucose (mmol/L)	10.6 (2.4)	10.6 (2.5)	0.2 (−0.6, 1.0)	9.4 (1.8)	9.1 (1.9)	−0.1 (−0.4, 0.3)	−0.9 (−1.6, −0.1) ^a
SD (mmol/L)	3.9 (1.1)	3.7 (1.0)	−0.1 (−0.5, 0.3)	3.9 (0.9)	3.8 (1.0)	0.0 (−0.2, 0.2)	0.1 (−0.3, 0.4)
CV (%)	37.2 (8.4)	36.0 (8.6)	−1.0 (−4.4, 2.3)	41.9 (8.9)	42.7 (10.5)	0.4 (−1.7, 2.5)	4.9 (1.0, 8.8) ^a
MAGE (mmol/L)	7.7 (2.6)	7.7 (2.2)	0.3 (−0.9, 1.5)	7.9 (2.5)	7.9 (2.7)	0.0 (−0.6, 0.6)	0.0 (−1.0, 1.0)
MODD (mmol/L)	3.9 (1.1)	4.3 (1.4)	0.5 (0.01, 1.0) ^a	4.1 (1.4)	4.2 (1.3)	0.0 (−0.3, 0.3)	−0.2 (−0.7, 0.3)

Data are presented as estimated mean (SD) or mean change (95% confidence interval) within and between groups as indicated.

^a $P < 0.05$.

CGM, continuous glucose measurement; CIPII, continuous intraperitoneal insulin infusion; CV, coefficient of variation; MDI, multiple daily injections; MAGE, mean amplitude of glucose excursions; MODD, mean of the daily differences; SC, subcutaneous; SMBG, self-measurements of blood glucose.

respectively) and a higher CV (4.7% [95% CI, 0.3, 9.2] and 5.0% [95% CI, 0.8, 9.2], respectively) during CGM compared with CIPII-treated patients (see Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/dia).

Results of the SMBG demonstrate that, after adjustment for baseline differences, the CV of the self-measured glucose concentration was 5.6% (95% CI, 1.2, 9.9) higher among patients using SC insulin compared with those using CIPII. The mean glucose level was lower for patients using MDI, but not for those using CSII (−0.8 mmol/L; 95% CI, −1.6, −0.1), compared with CIPII-treated patients. Adjusted for baseline differences, the CV of self-measured glucose concentrations was 6.5% (95% CI, 1.9, 11.2) higher among CSII-treated patients compared with subjects using CIPII.

Discussion

CIPII-treated patients had a lower CV compared with patients treated with SC insulin therapy. The magnitude of this effect was approximately 5% compared with both MDI- and CSII-treated patients; it was found during both CGM and SMBG and remained present after adjustment for baseline differences in HbA1c, hypoglycemic episodes, and total daily insulin dose. Although the finding of a lower CV, the primary measure of GV, confirmed our hypothesis that T1DM patients treated with CIPII have less GV compared with patients treated with SC insulin therapy, it should be noted that there were no differences in other indices of intra- and interday GV.

These findings may suggest a positive influence of CIPII therapy on GV and could well be explained by the pharmacokinetic and pharmacodynamic properties of insulin administered by the IP route. After IP administration, insulin takes approximately 15 min to reach its peak effect and allows blood glucose values to return to baseline values more rapidly with reproducible and more predictable insulin profiles compared with SC insulin injections.^{5,19–21} In addition, IP insulin improves the impaired glucagon secretion, also during exercise, and enhances hepatic glucose production in response to hypoglycemia.^{22–26} Although the exact mechanisms behind these latter two phenomena are unknown, it has been hypothesized that lower peripheral plasma insulin concentrations with CIPII may (partly) restore glucagon release or that CIPII increases hepatic sensitivity to glucagon or hepatic glucose utilization during hypoglycemia.^{22,26}

The present study confirms the results of three previous studies reporting less GV among CIPII-treated patients. The most recent study by Catargi et al.¹¹ demonstrated among 14 T1DM patients who were treated sequentially with CSII (using short-acting insulin lispro) and CIPII that there was a significant decrease of the SD of all SMBG measurements during a 45-day period: 3.8 versus 4.4 mmol/L. The results of the present study add to these data by describing different measures of GV, based on both (blinded) CGM and SMBG data, on two different occasions, in a large T1DM population during usual care circumstances. As all subjects were on their current mode of insulin administration for ≥4 years, this may suggest that the pharmacokinetic and pharmacodynamic properties of insulin administered by the IP route perpetuate over time. Although hypothetically this may also indicate that the course of the HbA1c level among CIPII-treated patients, which has been reported to decrease shortly after initiation of

CIPII but increases during long-term use, is due to other factors (e.g. compliance) than physiologic adaption to the effects of IP insulin.^{8–11,27–32}

At present, CIPII is a last-resort treatment option for selected patients, and indications include, among others, frequent episodes of severe hypoglycemia (especially combined with hypoglycemia unawareness). Although long-term CIPII treatment does not seem to offer further improvements of HbA1c and general quality of life compared with short-term results, treatment satisfaction remains high, and patients report fewer hypoglycemic events compared with previous SC insulin therapy. The effects on GV found in this study may well account for this discrepancy.³³

It should be mentioned that debate exists in literature concerning the “optimal” measure of GV. There is no consensus at the moment. Therefore, based on available literature we chose a limited set of indices and a primary outcome that adjusts for different levels of mean glucose concentrations.^{16,34} In addition, post hoc analysis demonstrated significant correlations among CV, MAGE, and MODD during both measurements (see Supplementary Table S2).

For the interpretation of the results of this study several limitations should be acknowledged. First and foremost, because CIPII is a last-resort treatment option for T1DM, the group of CIPII-treated patients is considered selected and more complex compared with SC-treated patients, and bias may well have occurred. Second, as there are no data available of GV during SC therapy prior to CIPII therapy in the current study, it can only be assumed that the presence of less GV among the CIPII group is due to CIPII. Furthermore, it should be acknowledged that the magnitude of the reduction (approximately 5%) is relatively small and was only observed for the CV and not for the other measures of GV. The number of measures of GV used was also limited. Because the clinical importance of GV with respect to diabetes-related complications (including quality of life) is unsure, the relevance of our findings with respect to clinical outcomes are unknown.^{12,13,35,36} Nevertheless, as current closed-loop systems using SC insulin therapy struggle to reach postprandial normoglycemia, the effects of IP insulin on GV may be of importance for the question of which route of insulin administration is the best for development for a closed-loop system.³⁷ Unfortunately, because of missing data of the exact timing and subsequent postprandial glucose patterns, this question remains unanswered in the current study.

In conclusion, CIPII-treated patients had a slightly lower CV compared with patients treated with SC insulin therapy. Furthermore, despite a higher mean glucose concentration among CIPII-treated patients, there were no differences in other indices of intra- and interday GV. These findings suggest a modest positive influence of CIPII on GV compared with SC insulin therapy. Future studies are needed to confirm these findings, in addition to the use of more measures of GV, in particular related to postprandial glucose patterns, and study whether this reduced variability results in prevention of hypoglycemia and possibly fewer microvascular complications.

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Author Disclosure Statement

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P.R.V.D. is responsible for the design, inclusion of patients, measurements, statistical analysis, and writing manuscript. K.H.G. is responsible for the design, statistical analysis, and critically reviewing manuscript. R.O.B.G. and J.H.D.V. critically reviewed the manuscript. N.K., H.J.G.B., and S.J.J.L. are responsible for design and critically reviewed the manuscript. P.R.V.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Address correspondence to:

Peter R. van Dijk, MD, PhD

Diabetes Centre

Isala

P.O. Box 10400

8000G.K. Zwolle, The Netherlands

E-mail: P.r.van.Dijk@isala.nl