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Use of Short-Term Real-Time Continuous Glucose Monitoring in Type 1 Diabetes Patients on Continuous Intraperitoneal Insulin Infusion: A Feasibility Study

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Abstract

Background: In diabetes, strict glycemic control reduces risk of complications. One mode of therapy is continuous intraperitoneal insulin infusion (CIPII). With CIPII, like all intensified treatment strategies, frequent assessment of glucose levels is mandatory. Real-time (RT)-continuous glucose monitoring (CGM) gives RT information without the need for multiple invasive measurements. In theory, CIPII combined with RT-CGM could provide near normal glucose profiles. The objective of this study is to investigate effectiveness and safety of RT-CGM in patients treated with intraperitoneal insulin through an implanted pump.

Methods: In an open-label, crossover, randomized study, effects of 6-day open RT-CGM use were studied in 12 type 1 diabetes patients on CIPII, with blinded RT-CGM used as a control. Primary outcome was time in euglycemia. Secondary outcomes included time in other glucose ranges, incidence of adverse events, and patient satisfaction. Agreement of self-measurement of blood glucose (SMBG) and RT-CGM measurements was assessed.

Results: Median time spent in euglycemia was 68.2% (55.9–72.3%) with open RT-CGM and 64.9% (55.3–71.2%) with blinded RT-CGM ($P = 0.25$). Time spent in other glucose ranges did not differ ($P > 0.05$). There were no serious adverse events. Patient satisfaction was good. Median relative absolute difference of SMBG and RT-CGM values was 13.9%. Bland-Altman analysis showed a mean difference of -0.31 mg/dL with lower and upper limits of agreement of -77.0 and $+76.4$ mg/dL, respectively.

Conclusions: Short-term use of RT-CGM, although safe and with good patient satisfaction, does not result in more time spent in euglycemia, nor does it change time spent in other glucose ranges in our population of type 1 diabetes patients receiving CIPII.

Introduction

STRICT GLYCEMIC CONTROL reduces the risk of complications in diabetes mellitus.^{1,2} To reach such control in type 1 diabetes mellitus, current treatment options are multiple daily injections (MDI), continuous subcutaneous insulin infusion (CSII), and continuous intraperitoneal insulin infusion (CIPII) using an implanted insulin pump. CIPII is mainly used in patients who, despite intensive subcutaneous insulin therapy, do not reach acceptable glycemic control

and/or have frequent hypoglycemic episodes (especially when accompanied by hypoglycemia unawareness) and/or have subcutaneous insulin resistance.³ At the moment CIPII is only available in a few European countries, mostly in France, Sweden, and The Netherlands.^{4,5}

All patients on insulin treatment, regardless the mode of administration, are instructed to perform self-measurement of blood glucose (SMBG) multiple times a day to evaluate insulin treatment and to obtain information about how to adjust their insulin regimen.⁶ SMBG is also advised when

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hypoglycemia or hyperglycemia is suspected. Still, intermittently performed blood glucose measurements can give only limited information on 24-h blood glucose profiles.

Another mode of measuring glucose, using continuous glucose monitoring (CGM), is now available. Potential trends in glycemic profiles that would normally be missed with SMBG can be identified.^{7,8} Real-time (RT)-CGM is a novel system that can provide the patient and the healthcare professional with information about the current glucose level without the need for multiple invasive measurements. In theory this would allow for near normal blood glucose profiles to be reached. RT-CGM has proven to be effective in reducing hyperglycemic and hypoglycemic excursions in ambulatory patients with type 1 diabetes mellitus.^{9–11} Most of these patients were treated with either MDI or CSII, with some receiving conventional insulin therapy.

Given the indications based on which patients are treated with CII, RT-CGM might be helpful in this particular patient category. Furthermore, the combination of an implanted intraperitoneal insulin delivery device and a continuous (subcutaneous) glucose sensor could be of importance in the development of a closed loop system, although the subcutaneous insulin delivery device–subcutaneous glucose sensor and intraperitoneal insulin delivery device–intravenous glucose sensor combinations are currently most studied.^{12,13} RT-CGM has never been tested in a population of outpatient type 1 diabetes mellitus patients treated with CII. The objective of this study therefore is to investigate the effectiveness and safety of RT-CGM in this patient category.

Subjects and Methods

Study population

Subjects with type 1 diabetes mellitus with less than adequate glycemic control, defined as hemoglobin A1c (HbA_{1c}) $\geq 7.5\%$ and/or five or more incidents of hypoglycemia (defined as SMBG measurement below 72 mg/dL [4.0 mmol/L]) per week, over 18 years of age, and treated with CII, were eligible for the study. Reasons for exclusion from the study were failure to obtain informed consent, any condition preventing proper handling of the device (for instance, hearing impairment or visual impairment), known allergy to sensor (parts), and currently pregnant or trying to conceive.

The study was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients, and the protocol was approved by the Medical Ethics Committee of the Isala Clinics (Zwolle, The Netherlands).

Study design

The study had a crossover, randomized design and was conducted in a single center (Isala Clinics) in The Netherlands. The study consisted of four periods: the baseline phase, the first study phase, the crossover phase, and the second study phase. After the baseline phase of 3 days, in which all subjects were blinded to sensor values, subjects were randomly allocated to one of two groups, differing in the order of the blinded and open mode of the RT-CGM device (Paradigm[®] REAL-Time system, Medtronic MiniMed, Northridge, CA). After informed consent was obtained, randomization was performed using sealed opaque envelopes, which indicated the assigned mode of RT-CGM in the first study phase; blind-

ed or open, respectively. Both study phases were 6 days in duration. A crossover phase of 1 week was instituted between the two study phases to minimize carryover effects. During the crossover phase, no RT-CGM system was used.

All patients were asked to perform SMBG (Accu-Chek[®] Aviva, Roche Diagnostics, Mannheim, Germany) at least four times daily (fasting, before meals, and before bedtime) and to perform SMBG seven times daily (fasting, before and after meals, and before bedtime) once every 3 days.

During the study, there were six scheduled contacts with a diabetes specialist nurse or a study investigator: the first and the last study contact were at the diabetes outpatient clinic, and the others were by telephone, at the start and halfway through both study phases. In addition to the scheduled contacts, subjects could contact a diabetes specialist nurse or a study investigator throughout the study in case of problems or questions at any time of the day.

During the first study visit, subjects were instructed about sensor insertion and calibration, after which the first sensor was inserted in the presence of the investigator or diabetes specialist nurse. All sensors were inserted by the subjects themselves. Each sensor was worn for a maximum of 72 h. In both study phases the first sensor was immediately replaced by the next. Subjects kept a study diary to record the number of SMBG performed, the number of performed sensor calibrations, device alarms, and other information regarding glucose control. Subjects were asked to perform sensor calibration four times per day using a blood glucose measurement taken in a period of stable blood glucose, i.e., fasting, before meals, or before bedtime.

During the open study phase, sensor alarms were set at 70 mg/dL (3.9 mmol/L) and 200 mg/dL (11.1 mmol/L). No treatment adjustments were to be based on sensor values alone; all patients were instructed to use SMBG values to guide therapeutic decisions. Subjects were allowed to adjust insulin dose during the whole study as they seemed fit to do without any restrictions.

During the last study visit, RT-CGM and SBMG data were downloaded into a computer, and patient satisfaction was assessed with a questionnaire.

Primary and other outcomes

The primary outcome measure was the percentage of time spent in euglycemia. Time spent in the different glucose ranges was calculated from RT-CGM data. Time spent in the euglycemic range was defined as percentage of CGM recordings between 71 and 180 mg/dL (4.0–10.0 mmol/L).

Secondary outcome measures were percentage of time spent in hypoglycemia and hyperglycemia, the incidence of adverse effects, patient satisfaction, and agreement of paired SMBG and RT-CGM measurements. Time spent in the hypo- and hyperglycemic range was defined as percentage of recordings below 70 mg/dL (3.9 mmol/L) and above 180 mg/dL (10.0 mmol/L), respectively. Patient satisfaction was assessed with a modified version of the User Acceptance Questionnaire for CGM as designed by Peyrot and Rubin.¹⁴ Next to items regarding the overall assessment of the device (six items), the questionnaire contains items regarding Comfort (six items), Sensor Operation (eight items), Sensor Use (five items), Alarms (11 items), and Glucose Control (seven items) on a 7-point Likert scale from 1 (strongly disagree) to 7

(strongly agree). Furthermore, patients were asked about satisfaction with glucose control and whether or not they regarded their glucose control improved with RT-CGM.

Demographic and clinical measurements

At baseline, demographic and clinical parameters were recorded, including age, sex, and year of diagnosis of diabetes. In addition, at baseline, fear of hypoglycemia was assessed with the validated Hypoglycemia Fear Survey (HFS).^{15,16} Aspects of diabetes self-care and outcome were rated, with questions regarding SMBG, current glucose control, and fear of hypoglycemia, on 4- or 5-point scales.

Sample size calculation and statistical analysis

To test our hypothesis that use of RT-CGM can provide a 15% absolute increase in time spent in euglycemia with 85% power and α 5% (two-tailed), a total sample size of 11 was required. These calculations were based on a standard deviation (SD) of 14.6 as derived from a previous study in which patients receiving CIPII used CGM.¹⁷

Descriptive summaries included mean (SD) for normal distributed variables and median with interquartile range for other variables. Normality was examined with Q-Q plots. Planned analyses were conducted to address the study objectives as defined, using a nominal significance level of 0.05. General linear models were used to test differences, taking treatment order into account.¹⁸ If assumptions for the general linear models were not met, nonparametric tests were used.

Agreement was evaluated from paired glucose values of SMBG and RT-CGM (time difference not more than 5 min) with median relative absolute difference (RAD) values and Bland-Altman analysis.¹⁹ Statistical analyses were performed with SPSS (Chicago, IL) software version 16.0. All reported *P* values are two-sided. Analyses were done according to the intention to treat principle.

Results

Patients

Figure 1 is the patient flow chart; 12 patients entered the study between December 2007 and March 2008. Characteristics of the subjects are listed in Table 1. Differences between groups were considerable, although not statistically significant because of small group sizes. Mean (SD) age was 43.8 (12.5) years. Mean (SD) HbA_{1c} level was 8.5% (1.3%). Median (range) time on CIPII was 17.5 (10.1–53.1) years. Median (range) percentage of time spent in euglycemia during the baseline phase was 43.7% (31.6–75.6%). Median (range) scores on the subscales of the HFS were 9.0 (7.0–22.0) and 11.0 (6.3–18.3) for the Behavior and the Worry subscale, respectively. Other patient reported outcomes are shown in Figure 2; subjects mostly regarded SMBG as never or sometimes painful and regarded the number of SBMG as about right or too often.

Primary outcome

Median (range) time spent in euglycemia was 68.2% (55.9–72.3%) during open RT-CGM use compared to 64.9% (55.3–71.2%) during blinded RT-CGM use (*P* = 0.25).

FIG. 1. Patient flow chart.

Secondary outcomes

Glucose ranges. In Figure 3 mean percentages of time spent in hyper-, hypo-, and euglycemia are shown for open and blinded RT-CGM use (*P* = 0.61 and *P* = 0.23 for difference in time spent in hypo- and hyperglycemia, respectively). More narrow glucose ranges are also shown; there are no significant differences in percentage of time in any of these glucose ranges between open and blinded RT-CGM use (*P* = 0.30 for 71–110 mg/dL, *P* = 0.43 for 111–155 mg/dL, *P* = 0.34 for 156–180 mg/dL, *P* = 0.70 for 181–210 mg/dL, *P* = 0.20 for 211–240 mg/dL, *P* = 0.47 for 241–270 mg/dL, *P* = 0.06 for 271–300 mg/dL, and *P* = 0.35 for >300 mg/dL).

TABLE 1. CHARACTERISTICS AT BASELINE

Characteristic	Of total n = 12
Age (years)	43.8 (12.5)
Male (n)	5
Diabetes' duration (years)	24.2 (9.7)
Time on CIPII (months) ^a	17.5 (10.1–53.1)
HbA _{1c} (%)	8.5 (1.3)
Time spent in glucose range (%) ^a	
Hypoglycemia	0.0 (0.0–1.9)
Euglycemia	43.7 (31.6–75.6)
Hyperglycemia	54.3 (23.9–68.4)
Fear of hypoglycemia ^a	
Total score (range 0–112)	20.0 (12.0–35.0)
Behavior subscale (range 0–60) ^b	9.0 (7.0–22.0)
Worry subscale (range 0–52)	11.0 (6.3–18.3)

Data are mean (SD) or number of subjects unless otherwise indicated.

^aMedian (interquartile range).

^bOne subject (blinded RT-CGM in first phase) left one question unanswered on the Behavior subscale.

FIG. 2. Patient-rated response at baseline ($n = 12$).

Adverse events. Patients reported no serious adverse events during either study phase. There was one report of redness of the skin, and two patients reported itching. There was one report of hematoma after sensor insertion; it was noticed only hours after sensor insertion, reached a maximum diameter of approximately 5–10 cm (patient report), and did not require further action. None of these reports required termination of the study or replacement of the sensor.

Agreement of paired SMBG and CGM measurements. Figure 4 shows the scatter plot of SMBG-derived glucose values versus CGM-derived glucose values and the Bland-Altman plot. Mean difference (bias) is -0.31 mg/dL (-0.02 mmol/L) with lower and upper limits of agreement of -77.0 and $+76.4$ mg/dL (-4.28 and $+4.24$ mmol/L), respectively. The scatter of the differences increases with increasing glucose values. Median RAD was 13.9% for all comparisons ($n = 980$). Median RAD was least for hyperglycemic values

(12.4%; $n = 331$), was 15.3% ($n = 630$) for euglycemic values, and was 25.6% for hypoglycemic values ($n = 19$).

Number of sensor alarms. Mean number of sensor alarms during open RT-CGM use was 6.6 (3.2) per day. Most of these were “High glucose” alarms (89.5%). Two patients turned the “High glucose” alarm off during part of the open RT-CGM phase; one subject turned off the alarm during the nights starting the third night and received 12.5 (4.0) alarms per day during the whole open RT-CGM phase. The other patient turned off the “High glucose” on the fourth day for the rest of the phase, after receiving a mean of 9.3 alarms per day during the first half of the phase.

Patient satisfaction and user acceptance. Mean (SD) User Acceptance Questionnaire scores regarding Comfort, Sensor Operation, Alarms, Glucose Regulation, Sensor Use, and Overall Assessment (range 0–100) were 75.0 (13.5), 67.2

FIG. 3. (Left) Time in hypo-, eu-, and hyperglycemia, respectively ($P > 0.05$ for all comparisons). (Right) Percentages of time in more narrow glucose ranges ($P > 0.05$ for all comparisons).

FIG. 4. (Left) Scatter of SBMG-derived glucose values versus CGM-derived glucose values during the whole study ($n=980$). (Right) Bland-Altman plot. Horizontal lines in the right panel are drawn at bias (-0.31 mg/dL) and lower and upper limits of agreement (-77.0 and $+76.4$ mg/dL, respectively).

(20.3), 60.6 (14.4), 52.8 (19.6), 70.8 (14.0), and 59.7 (20.8), respectively. Figure 5 shows patient satisfaction in more detail; mean scores on each item are shown. Eight out of 12 subjects rated their glucose control as improved with the open RT-CGM. When asked whether subjects would recommend use of RT-CGM to other patients with diabetes, 83% would indeed recommend it, although 80% of those would recommend intermittent use instead of permanent use of RT-CGM.

Conclusions

Short-term use of RT-CGM does not result in more time spent in euglycemia as compared to blinded RT-CGM use, nor

does time spent in other blood glucose ranges change with use of open RT-CGM in type 1 diabetes patients treated with intraperitoneal insulin infusion. RT-CGM proved to be safe regarding local complications or adverse events.

To our knowledge, this is the first trial that investigated RT-CGM use in CIPII. RT-CGM has been evaluated in other populations with mixed results. A recent meta-analysis showed no effect of retrospective readings of CGM on HbA_{1c} in children.²⁰ The authors stressed that their conclusion should be interpreted with caution because of methodological weaknesses of the trials included. Others have found positive effects of short term RT-CGM use. Garg et al.¹¹ reported from their controlled study of two 3-day courses of RT-CGM use an

FIG. 5. Mean (standard error) scores on all items of the modified User Acceptance Questionnaire. A higher score represents more positive answers.

increase in time spent in the target range (81–140 mg/dL [4.5–7.8 mmol/L]) from 5.52 to 6.98 h/day in diabetes patients receiving either CSII or MDI. This 6% absolute increase in percentage of time spent in euglycemia is comparable with the results of our current study.

In an earlier study with an implanted RT-CGM, time spent in the target range increased from 19.8% during the blinded period (mean duration, 50 days) to 37.1% during the following open CGM phase (mean duration, 44 days).¹⁰ Regarding other outcome parameters, only Deiss et al.²¹ were able to report HbA_{1c} improvement in a randomized controlled study; compared to use of SMBG only, continuous use of RT-CGM for 3 months resulted in an 0.6% HbA_{1c} decrease (from 9.5% to 8.5%).

Like us, Peyrot and Rubin¹⁴ reported positive user acceptance scores of RT-CGM in type 1 diabetes patients just starting with CSII.

Our results regarding device agreement are in line with previous reported accuracy rates of RT-CGM devices; Garg et al.¹¹ reported an overall median RAD for the STS (Dex-Com™, San Diego, CA) of 15.9%. In a recently published study, Kovatchev et al.²² reported a median RAD of the Guardian RT (Medtronic MiniMed) of 13.3% in euglycemia. A study with the Navigator® (Abbott Diabetes Care, Alameda, CA) in children (outpatients) provided a similar pattern of accuracy across different glucose ranges, with 26% for the hypoglycemic range, 10% for the hyperglycemic range, and 13% for the euglycemic range.²³ Our results also indicate that accuracy of RT-CGM falls somewhat behind that of SMBG. Optimal use of RT-CGM will therefore require specific education of patients and healthcare providers.²⁴ We note that in our trial only 1.9% of sensor values were in the hypoglycemic range, and therefore we cannot provide a definite conclusion about the performance of the sensor in that range.

There are some weaknesses of this study. Our study is of limited duration and includes only a limited number of subjects; extended use of the RT-CGM device might lead to other results and would enable determination of the effects on HbA_{1c} and severe hypoglycemic events. The limited number of subjects has also resulted in slightly unequal groups at baseline, despite adequate randomization procedures. Second, in the open RT-CGM phase, the alarms were set at prespecified levels, and subjects were not encouraged to alter the settings. However, two subjects felt so much bothered by the “High glucose” alarm, especially during nights, that changes were made. One patient indicated that the frequency of alarms was a nuisance and that he was sufficiently informed about his glucose level by looking at the graph frequently. In the other patient, high glucose levels during nights were without direct treatment consequences and interfered with night rest. We did not give treatment algorithms to subjects in this feasibility study. This might have prevented adequate reaction on sensor information. However, in order to be eligible for CIPII in the Netherlands, patients receive extensive diabetes education, and a high level of diabetes self-management is mandatory. Future studies should include study arms with prespecified treatment algorithms.

Although subjects were included based on objective inadequate glycemic control, most subjects rated their glycemic control as moderate or good and did not worry often about hypoglycemic events. Despite the absence of an objective improvement in glycemic control, two-thirds of patients re-

garded their glucose control improved with the use of RT-CGM, and almost all would recommend it to other patients. It seems that other aspects of RT-CGM use appeal to patients.

The questionnaire at baseline revealed a fairly positive attitude towards SMBG and low fear of hypoglycemia compared to a population of Dutch type 1 diabetes patients treated with MDI or CSII (Worry HFS score, 30.5 [12.5]).²⁵ The former might have been partly responsible for the lack of effect of RT-CGM, and the latter might be explained by specific aspects of intraperitoneal insulin therapy, including more predictable insulin profiles and better absorption.^{26,27}

We conclude that RT-CGM can be used safely in patients treated with CIPII but that there is no effect on glucose control, at least with short-term use. Whether long-term use would alter this conclusion remains to be investigated. Regarding the ongoing development of a fully closed loop system, we suggest not ruling out the intraperitoneal insulin delivery device–subcutaneous glucose sensor combination as a viable option.

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Author Disclosure Statement

There are no competing financial interests.

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