

Combined Insulin Pump Therapy with Real-Time Continuous Glucose Monitoring Significantly Improves Glycemic Control Compared to Multiple Daily Injection Therapy in Pump Naïve Patients with Type 1 Diabetes; Single Center Pilot Study Experience

Scott W. Lee, M.D., Tom Sweeney, R.N. N.P., Debbie Clausen, R.N. N.P., Celia Kolbach, R.N., Allen Hassen, M.D., Anthony Firek, M.D., Charles Brinegar, M.D., and Jerrold Petrofsky, Ph.D.

Abstract

Objectives:

This study assessed the safety and clinical effectiveness of the training protocol for initiating insulin pump therapy with real-time continuous glucose monitoring (MiniMed Paradigm REAL-Time System) in a stepwise approach on pump naïve subjects with type 1 diabetes compared to a control group who remained on multiple daily injection (MDI) therapy.

Methods:

This was a 15-week treat-to-target pilot study of 16 adult subjects ($n = 50\%$ male, age 45.9 ± 16 years) with type 1 diabetes (duration of diabetes 21.9 ± 11 years) on MDI therapy with hemoglobin A1c levels at or above 7.5% at baseline. Subjects were randomized to either the study arm (using a combined insulin pump and real-time continuous glucose monitoring system) or the control arm [which continued on MDI therapy with self-monitored blood glucose (SMBG) only]. All subjects dosed insulin according to results of SMBG by finger stick and uploaded data into the CareLink data management software.

Results:

Significant improvements in glycemic control were observed from baseline in both study groups—study arm: pre-A1c 9.45 ± 0.55 and post-A1c 7.4 ± 0.66 ($p = 0.00037$); control arm: pre-A1c 8.58 ± 1.30 and post-A1c 7.5 ± 1.01 ($p = 0.04$). Both arms had no incidence of severe hypoglycemia.

Conclusion:

In this pilot study, the Paradigm REAL-Time System was initiated safely and effectively in type 1 diabetes patients who were pump naïve using a stepwise educational protocol.

J Diabetes Sci Technol 2007;1(3):400-404

Author Affiliation: Loma Linda University School of Medicine, Diabetes Treatment Center, Loma Linda, California

Abbreviations: (ADA) American Diabetes Association, (CGM) continuous glucose monitoring, (CSII) continuous subcutaneous insulin infusion, (DCCT) Diabetes Control and Complications Trial, (MDI) multiple daily injection, (RT-CGM) real-time continuous interstitial glucose monitoring, (SAE) serious adverse events, (SMBG) self-monitored blood glucose

Keywords: augmented, diabetes, sensor, pump, real time, paradigm

Corresponding Author: Scott W. Lee, M.D., Diabetes Treatment Center, 11285 Mountain View Ave., Suite 40, Loma Linda, CA 92354; email address Slee@ahs.llumc.edu

Introduction

Sensor-augmented insulin pump therapy is a convergence of two technologies: continuous insulin infusion therapy and real-time continuous interstitial glucose monitoring (RT-CGM). A large body of evidence in the last decade has been published on both of these technologies separately, but no randomized studies have been published to date on the integration of these technologies when initiated in patients with type 1 patients who are pump naïve.

The Diabetes Control and Complications Trial (DCCT)¹ highlighted the importance of intensive insulin therapy in lowering ambient glucose to near-normal levels in persons with type 1 diabetes mellitus in order to prevent long-term microvascular complications, and the Epidemiology of Diabetes Interventions and Complications study established that early control of diabetes also significantly reduces the risk of macrovascular^{2,3} complications. Results of the DCCT trial prompted the American Diabetes Association (ADA) to recommend that the hemoglobin A1c should be <7%.⁴

The ADA targets for glucose control can be difficult to attain.¹ The incidence of hypoglycemic reactions was threefold higher in the DCCT as patients approached an A1c of 7.2%.¹ Thus, the major limiting factor to reaching optimal glycemia for many individuals with diabetes is the incidence of hypoglycemia.⁵ In prior studies, utilization of continuous subcutaneous insulin infusion (CSII) has demonstrated significant reductions in both the quality and the quantity of hypoglycemia.⁶⁻⁸ A comprehensive meta-analysis of 52 studies supported improvement of glycemic control with CSII compared with conventional therapy of multiple daily injections (MDI), coupled with qualitative reductions in hypoglycemia.⁹

Frequent self-monitoring of blood glucose (SMBG) is a critical component of intensive therapy with insulin pumps and assists patients in their estimation of insulin dosing, food intake, and exercise.¹ SMBG, however, cannot be performed frequently enough to reliably detect every glycemic excursion.¹⁰ Continuous glucose monitoring (CGM) can be used to improve glucose control by capturing clear trends in the patients' glycemic profiles that are not easily identified by intermittent SMBG alone.^{11,12} On retrospective analysis of patients wearing CGM, we found that 96% of patients had hyperglycemia and 63% had hypoglycemia that was not detected by SMBG. Information from CGM resulted in 92% of patients having a medication change.¹³

More recently, continuous glucose monitoring has given patients the added ability of viewing their glucose real time, as well as reviewing graphs of recent trends in their glycemic control.¹⁴ The application of real-time alarms warns users of impending hypo- and/or hyperglycemia, thereby potentially allowing for either preventative or, if need be, corrective action.^{10,11} Data from long-term implantable sensors have demonstrated reduced glucose excursions when real-time continuous glucose values were available to patients with type 1 diabetes.¹⁵ Given the established evidence in the medical literature on the efficacy of glucose control with insulin pump therapy and the emerging positive balance of data on RT-CGM, we anticipated that patients who were pump naïve and on MDI would benefit when transitioned to the combined use of real-time glucose monitoring integrated with insulin pump therapy (Paradigm REAL-Time 722 System).

Methods

Study Design

This was a two-center, treat-to-target pilot study evaluating the educational protocol for initiating sensor-augmented pump therapy on pump naïve subjects. At this study site, 16 adult subjects ($n = 8$ males), age 45.9 ± 16 years, with type 1 diabetes (duration of diabetes 21.9 ± 11 years) on MDI therapy who were insulin pump naïve with A1c levels at or above 7.5% were randomized to either the study arm, which used a combined insulin pump and real-time CGM system as an adjunct to SMBG, or a control arm, which remained on MDI with SMBG-only therapy for the duration of the 15-week study.

Educational Protocol

All subjects received carbohydrate counting education and a review of basic diabetes self-management training (i.e., how to treat high and low glucose) at the first visit. Both study arms were educated on how to use the CareLink data management system and were instructed to upload all available data on a weekly basis. During study visits, both arms were given specific glucose targets and provided guidance on how to interpret and understand the various reports and graphs that were available to them. All subjects were encouraged to look for opportunities to make therapy changes that would improve their control and were invited to contact the clinic staff for support.

The MDI arm had four visits total after randomization. At the second visit, 2 weeks after the first visit, the use

of insulin coupled with downloaded information from CareLink was reviewed. Insulin adjustments were made. At week 5, this same procedure was repeated as the last visit. At their final visit on week 15, CareLink data and use of insulin were reviewed and recorded.

The study group had three additional clinic visits early in the protocol specifically focused on initiation of pump therapy and RT-CGM. The study arm used a stepwise approach to initiation of the combined insulin pump with real-time continuous glucose monitoring over a 3-week period. At the first visit after randomization, subjects were instructed to complete, at home, a computer-based training course on insulin pump therapy. This training included (1) basics on insulin pump *therapy*, such as basal/bolus concepts, blood glucose target ranges, and insulin sensitivity; and (2) basics on pump *features*, including how to program the pump, how to use the Bolus Wizard® calculator, the importance of using the Bolus Wizard for all meals and correction doses, and the use of infusion sets and reservoir. At the second visit, 2 days later, insulin pump therapy was initiated. Subjects were required to present their certificate of training from the computer program and to demonstrate proficiency with the device.

Initial pump settings were individualized for subjects within the following parameters: (1) glucose target ranges of 90–120 mg/dl from 7 a.m. to 10 p.m. and 100–120 mg/dl from 10 p.m. to 7 a.m.; (2) insulin sensitivity factor was individualized for each patient so that 1 unit of correction was given for every 30–50 mg/dl above a target range; (3) insulin-to-carbohydrate ratios were calculated individually based on the patient's total daily dose of insulin and some patients had a reduced ratio of 30–50% between the time of 10 p.m. to 7 a.m. to avoid hypoglycemia; (4) active insulin time was set at 3 hours; and (5) basal rate settings were initially set highest in the 3 to 6 a.m. (dawn) period.

Three days after pump initiation, the study arm returned for a third visit to assess how they were doing on the insulin pump. Two weeks after randomization (fourth visit) each patient returned to the clinic for initiation of real-time continuous glucose monitoring therapy. Comprehensive patient education covered the following technical and therapeutic elements. The major points were as follow: (1) sensors were to be worn *at least* 5 days every week, with each sensor to be worn for a maximum of 72 hours; (2) four capillary (finger stick) blood glucose measurements were required each day using the Paradigm Link® glucose meter; (3) instruction on sensor insertion and calibration was provided with the requirement that patients demonstrate competence; (4) treatment

for hypoglycemia and/or hyperglycemia must be based on the results of capillary blood glucose values (finger sticks), not on sensor values; (5) while continuous glucose monitoring and blood glucose are both accurate ways to measure glucose, at any moment in time, exact readings will rarely match, especially when the glucose levels are rising or falling rapidly^{16–18}; (6) focus less on the actual numbers and more on the trends (velocity and direction) of the glucose readings; and (7) the importance of *always* using the bolus calculator in order to prevent dangerous hypoglycemia.

The RT-CGM can be set to sound an alarm when glucose levels get too high or too low, and the snooze alarm feature can be programmed to silence the alarm for a period of time. At the beginning of the study the alarm settings were set at a low of 80 mg/dl and a high of 200 mg/dl, with the corresponding snooze feature set for 20 minutes for low alarms and 1 hour for high alarms. These high alarm settings were adjusted 8 weeks into the study after complaints that recurrent night time alarms were interfering with sleep. After the high alarm setting was adjusted to sound an alarm when glucoses reached 250 mg/dl and the snooze was set for 2–3 hours, the complaints ceased.

Visits 5 and 6 occurred 3 and 5 weeks after randomization, respectively. At these visits, uploaded data on CareLink were used to help make therapy adjustments as needed to improve glycemic control. Because CareLink reports provide retrospective data on timing and amount of insulin relative to a meal with concurrent postprandial response, bolus calculator settings were adjusted easily. Visit 7 was the last visit (15 weeks from randomization) wherein CareLink reports were reviewed and overall subject status was reviewed.

Statistics

Given the small sample size ($n = 16$), nonparametric statistical measures were performed, and it is important to note that this pilot study was not powered for comprehensive statistical analysis. The Wilcoxon signed-rank test was used for comparison between baseline and 16-week A1c. The Mann–Whitney test was applied for comparing the change in A1c between the control arm and those on sensor-augmented pump therapy.

Results

Significant improvements in glycemic control were observed from baseline compared to 15 weeks in both study groups—study arm: pre-A1c 9.45 ± 0.55 and post-A1c 7.4 ± 0.66 ($p = 0.00037$); control arm: pre-A1c 8.58 ± 1.30

Table 1. Hemoglobin A1c Results

Study arm, <i>n</i> = 8 (pump therapy with real-time CGM)			Control arm, <i>n</i> = 8 (multiple daily injection therapy)		
A1c at baseline	A1c at 15 weeks	A1c change	A1c at baseline	A1c at 15 weeks	A1c change
9.45 ± 0.55	7.4 ± 0.66	-2.05	8.58 ± 1.30	7.5 ± 1.01	-1.08
<i>p</i> = 0.0004			<i>p</i> = 0.04		
					Δ between groups: <i>p</i> = 0.02

and post-A1c of 7.5 ± 1.01 (*p* = 0.04) (Table 1). There were two serious adverse events (SAE) in the control group involving the same subject. The first SAE was diabetic ketoacidosis associated with atypical chest pain and the second was related to food poisoning, which resulted in uncontrolled diabetes and hypoglycemia.

Conclusion

This is the first randomized, controlled study to assess the effectiveness of initiating the use of a combined insulin pump and real-time CGM system in type 1 patients who are pump naïve. We report that in this pilot study the Paradigm REAL-Time System enabled participants with type 1 diabetes to achieve greater reductions in A1c levels than what patients maintained on MDI achieved, and these greater reductions occurred without incidence of severe hypoglycemia. Criteria for the sensor-augmented pump were similar to pump therapy (Table 2). The improvement in glycemia seen in both groups may be explained by the number of clinician visits, as well as the review of diabetes education that occurred. While the magnitude of the A1c improvement from baseline was greater in the study arm (-2.05) compared to the control arm (-1.08),

it is important to note that the study arm had a higher initial A1c average and a greater number of clinician visits as necessitated by initiation of the pump and RT-CGM therapy (study arm had eight visits whereas control arm had five visits). Future analysis of data collected during this study may explore sensor utilization rates, glycemic variation over time, patient satisfaction surveys, and quality of life measures.

References:

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993 Sep 30;329(14):977-86.
2. The Epidemiology of Diabetes Interventions and Complications (EDIC) Study. Sustained effect of intensive treatment of type I diabetes mellitus on development and progression of diabetic nephropathy. *JAMA.* 2003 Oct 22;290(16):2159-67.
3. Nathan DM. Effect of intensive diabetes management on cardiovascular events in type I diabetes. Proceedings of the 65th Annual Scientific Sessions of the American Diabetes Association; 2005 June 10-14; San Diego, CA. Alexandria (VA): American Diabetes Association.
4. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care.* 2003;26:S33-50.
5. Cryer PE, Davis SN, Shamon H. Hypoglycemia in diabetes. *Diabetes Care.* 2003 Jun;26(6):1902-12.
6. Reynolds LR. Reemergence of insulin pump therapy in the 1990s. *South Med J.* 2000 Dec;93(12):1157-61.
7. Boland EA, Grey M, Oesterle A, Fredrickson L, Tamborlane WV. Continuous subcutaneous insulin infusion. A new way to lower risk of severe hypoglycemia, improve metabolic control, and enhance coping in adolescents with type 1 diabetes. *Diabetes Care.* 1999 Nov;22(11):1779-84.
8. Bode BW, Steed RD, Davidson PC. Reduction in severe hypoglycemia with long-term continuous subcutaneous insulin infusion in type 1 diabetes. *Diabetes Care.* 1996 Apr;19(4):324-7.
9. Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R. Insulin pump therapy: a meta-analysis. *Diabetes Care.* 2003 Apr;26(4):1079-87.
10. Bremer T, Gough DA. Is blood glucose predictable from previous values? A solicitation for data. *Diabetes.* 1999 Mar;48(3):445-51.
11. Bode B, Gross K, Rikalo N, Schwartz S, Wahl T, Page C, Gross T, Mastrototaro J. Alarms based on real-time sensor glucose values alert patients to hypo- and hyperglycemia: the guardian continuous monitoring system. *Diabetes Technol Ther.* 2004 Apr;6(2):105-13.

Table 2. Criteria for Sensor-Augmented Pump Therapy Are Similar to Pump Therapy

Inadequate glycemic control, defined as A1c above target (>7%)

“Dawn phenomenon,” with glucose levels greater than 144–162 mg/dl (>8–9 mmol/liter) in the morning

Marked daily variations in glucose levels

History of hypoglycemia unawareness or of hypoglycemic events requiring assistance

Need for flexibility in lifestyle

Pregnancy or intention to become pregnant

Note: Patients must be willing and able to meet the routine demands of pump therapy, such as the need to change the infusion set regularly and to monitor blood glucose at least four times a day

12. The Canadian Coordinating Office for Health Technology Assessment (CCOHTA): Continuous glucose monitoring in the management of diabetes mellitus. *Issues in Emerging Health Technologies* 32, 2002. Available online at www.ccohta.ca.
13. Lee S, Freitas M, Petrofsky JS, Chao E, Gomez L, Im R, Magbual R. Glucose excursions detected by the continuous glucose monitoring system and missed by routine self-monitoring blood glucose measurements in patients with type 1 and type 2 diabetes requiring insulin. *Diabetes*. 2004;53:A105.
14. Gross T, Kayne D, King A, Rother C, Juth S. A bolus calculator is an effective means of controlling postprandial glycemia in patients on insulin pump therapy. *Diabetes Technol Ther*. 2003;5(3):365-9.
15. Garg SK, Schwartz S, Edelman SV. Improved glucose excursions using an implantable real-time continuous glucose sensor in adults with type I diabetes. *Diabetes Care*. 2004 Mar;27(3):734-8.
16. Rebrin K, Steil GM, van Antwerp WP, Mastrototaro JJ. Subcutaneous glucose predicts plasma glucose independent of insulin: implications for continuous monitoring. *Am J Physiol*. 1999 Sep;277(3 Pt 1):E561-71.
17. Steil GM, Rebrin K, Mastrototaro J, Bernaba B, Saad MF. Determination of plasma glucose during rapid glucose excursions with a subcutaneous glucose sensor. *Diabetes Technol Ther*. 2003;5(1):27-31.
18. Tavis, DR. The public health impact of the MiniMed Continuous Glucose Monitoring System (CGMS)-an assessment of the literature. *Diabetes Technol Ther*. 2004 Aug;6(4):518-22.
19. Bode BW, Sabbah HT, Gross TM, Fredrickson LP, Davidson PC. Diabetes management in the new millennium using insulin pump therapy. *Diabetes Metab Res Rev*. 2002 Jan-Feb;18 Suppl 1:S14-20.
20. Lee SW, Im R, Magbual R. Current perspectives on the use of continuous subcutaneous insulin infusion in the acute care setting and overview of therapy. *Crit Care Nurs Q*. 2004 Apr-Jun;27(2):172-84.