

Feasibility of 10-Day Use of a Continuous Glucose Monitoring System in Adults with Type 1 Diabetes

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Background-the purpose of this pilot study was to evaluate feasibility of 10-day use of a transcutaneous, real-time, continuous glucose monitoring (cgm) system. All previous reports using different cgm systems were for 3, 5, or 7-day use.

Methods-On Day1, subjects received the CGM device (SEVEN® System) and underwent training on proper use. Subjects returned to the clinic on Days2, 7 and 10 for in-clinic sessions. On Days2 and 7, half of the subjects performed fingersticks every 15minutes and the other half had YSI samples drawn every 15minutes. On Day10, subjects participated in an 8-hour in-clinic session with YSI and fingerstick testing.

Results-The MARD for CGM vs. YSI was 12.6%, 11.3%, and 14.5% on Days2, 7, and 10, respectively (p=0.63). The CGM compared with SMBG performed better on Day10.

Conclusions-This is the first study that documents usability for 10 days of a CGM system was stable.

Abbreviations: AD-Absolute difference; ADA-American Diabetes Association; A1c-Hemoglobin A_{1c} ; CGM- Continuous glucose monitoring; CSII- Continuous subcutaneous insulin infusion (insulin pump); DCCT- Diabetes Control & Complications Trial; SMBG- Self-monitored blood glucose; MDI- Multiple daily injections; YSI - Yellow Springs Instrument; Type 1 Diabetes- Insulin dependent diabetes mellitus

Improvement in metabolic control, as measured by reduction in A1c levels, has been shown to decrease the incidence and progression of both micro- and macrovascular diabetic complications [1-5]. Hypoglycemia is the main limiting factor in achieving target A1c values for subjects with type 1 diabetes [6] and SMBG is an integral part of intensive diabetes management [7]. Recent availability of CGM devices has allowed patients to view real-time glucose values, glucose trends, and receive alarms/alerts of impending hypo- or hyperglycemia [8-12].

RESEARCH DESIGN AND METHODS

The protocol was approved by the IRB, and all 30 (20 females) adult subjects with type 1 diabetes signed informed consent. Mean \pm SD age and duration of diabetes were 35.3 ± 7.8 years and 22.3 ± 8.4 years, respectively. Sixteen subjects were using MDI, and 14 were on insulin pumps.

All subjects came to the clinic on Day 1 for sensor insertions and training. Sensor replacements were allowed within 72 hours of the initial insertion. Two patients had to replace their sensors within 72 hours due to dislodgement of the sensor. In instances where the sensor shut off prematurely, subjects were allowed to “re-start” the same initial sensor (one patient had to restart the sensor within 8 hours).

All 30 subjects also participated in a 6-hour in-clinic session on Day 2. Half of the subjects performed comparative fingersticks once every 15 minutes; the other half underwent peripheral venous catheterization for YSI samples every 15 minutes. Twenty-eight subjects returned to the clinic for In-clinic Day 7. The subjects who performed SMBG fingersticks on Day 2, now underwent peripheral venous catheterization, and vice versa. At the end of the 6-hour In-clinic day, subjects stayed for an extra 2 hours to restart

and calibrate their sensors for extended use. At home patients were asked to do similar fingersticks to assure accuracy of the sensors. Twenty-four patients returned for an 8-hour In-clinic session on Day 10 during which all patients underwent peripheral venous catheterization and had YSI samples drawn every 15 minutes. Two sensors failed prematurely between 72-96 hours and four other patients could not attend the in-clinic session on Day 10 because of schedule conflicts and/or bad weather in Denver. All patients also did SMBG every 15 minutes. At the end of the 8-hours all sensors were removed and sensor insertion site assessments were made for any skin irritation/infections.

The SEVEN sensor unit consists of an applicator, sensor probe, and transmitter housing as previously described [11,12]. After initial calibrations at two hours, patients were instructed to upload at least 1 SMBG value every 12 hours when glucose values were stable. Once calibrated, the receiver displayed glucose values that were updated at 5-minute intervals. The high glucose alert was set at 200 mg/dL and the low glucose alert was set at 80 mg/dL. All receivers were downloaded on Day 10 for data analyses.

Statistical Analysis Methods: Categorical variables such as patient diabetes history and baseline characteristics are summarized using counts and percentages. Kruskal-Wallis nonparametric test is used to compare CGM System accuracy at different times of sensor wear. Analyses were performed using SAS® Software, version 9.1.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Of the 1,050 paired points in reference to YSI measurements collected, 1,017 were between 40 and 400 mg/dL; (range of glucose values used in this study) and were analyzed prospectively for different statistics by using sensor glucose values as displayed to subjects

in real-time. Sensor performance was stable across 10 days of sensor wear (Table 1). There is no appreciable difference in the overall accuracy results; Table: Correlation Coefficient, Absolute Difference (AD), and Absolute Relative Difference (ARD) including all the paired data points (Kruskal-Wallis test $p > 0.05$), with minor changes in the Relative Difference (Kruskal-Wallis test $p = 0.02$). Median and Inter-quartile Range of AD to YSI measurement was 11.8 ± 20.9 mg/dL in the hypoglycemic; <70 mg/dL, 13.5 ± 19.5 in the euglycemic; $70-180$ mg/dL, and hyperglycemic 30.5 ± 54 mg/dL; >180 mg/dL, ranges respectively. Median and Inter-quartile Range of Absolute Relative Difference (ARD) to YSI measurement was 22.0 ± 37.9 % in the hypoglycemic (<70 mg/dL), 11.8 ± 17.8 % in the euglycemic ($70-180$ mg/dL), and hyperglycemic 12.8 ± 14.6 % (>180 mg/dL), respectively. The hypoglycemic alert used in this study was set at 80 mg/dL (considered clinically inadequate). This low alert detected hypoglycemia (<80 mg/dL) with 61 % sensitivity, 91 % specificity, and with a positive predictive value of 90 %. In comparison with SMBG, the CGM performed slightly better on Day 10 in AD (median of 15.5 mg/dL, $p = 0.03$, Table). However ARD was slightly higher on Day 10 when compared with SMBG.

The sensor performance was stable throughout ten days of use at home, when data was compared with SMBG values. More than 90 % of paired glucose readings fell within the clinically relevant Clarke's A and B Zones as reported previously with 3 and 7 day use of sensors (Figures 1a and 1b are available in an online appendix at <http://care.diabetesjournals.org>).

There were no sensor insertion site infections. Over the 10-day duration of this study, there were 7 incidences of sensor insertion site effects. Two instances of mild erythema with sensor adhesives and one

patient reported mild bruising at the sensor site.

CONCLUSIONS

This is the first report on the use of a transcutaneous CGM that lasts for 10 days. The SEVEN system, when used for 10 days (currently approved for 7 days), was safe (off-label), and well tolerated, with no skin reactions. The MARD for CGM vs. YSI was 12.6 %, 11.3 % and 14.5 % on days 2, 7 and 10, respectively and did not differ over the study duration ($p = 0.63$). The sensor performance was stable for 10 days when compared with SMBG values. Most CGM devices had reported similar sensitivity levels for detecting hypoglycemia and this needs to be improved in future CGM devices. The longer use of a sensor may result in better compliance and health outcomes and will be cost effective for an extra 3 day use of a 7 day sensor. Increased sensor use has been correlated with better A1c reductions in recent clinical trials [10-15]. This is the first study that documents that longer (10 days) sensor usage is feasible, safe, and practical. Long-term impact of 10 day use of SEVEN on A1c and hypoglycemia needs to be evaluated.

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Table: Differences in Glucose Values (mg/dL) from CGM in Reference to YSI and SMBG

| YSI In-Clinic Days 2, 7 & 10 ^ψ | | No. of Paired Data Points | Absolute Difference***(mg /dL) | | Relative Difference** (%) | | Absolute Relative Difference*(%) | |
|--|----|---------------------------|--------------------------------|-------------|---------------------------|-------------|----------------------------------|-------------|
| | | | Mean (SD) | Median | Mean (SD) | Median | Mean (SD) | Median |
| Overall | | 905 | 25.2(25.4) | 17.3 | 5.0(27.3) | 1.4 | 17.9(21.2) | 12.9 |
| Day† | 2 | 271 | 23.6(21.1) | 16.5 | -0.1 (18.3) | -1.2 | 14.4(11.3) | 12.6 |
| | 7 | 227 | 21.2(21.0) | 16.0 | 4.5(20.5) | 1.7 | 15.7(14.0) | 11.3 |
| | 10 | 407 | 28.4(29.7) | 18.8 | 8.7(34.3) | 1.6 | 21.6(27.9) | 14.5 |
| P-value | | | 0.08 | | 0.02 | | 0.63 | |
| SMBG In-Clinic Days 2, 7 & 10 ^χ | | No. of Paired Data Points | Absolute Difference***(mg /dL) | | Relative Difference** (%) | | Absolute Relative Difference*(%) | |
| | | | Mean (SD) | Median | Mean (SD) | Median | Mean (SD) | Median |
| Overall | | 1130 | 27.0(28.0) | 18.0 | -0.9(26.3) | -4.9 | 17.7(19.5) | 13.3 |
| Day† | 2 | 379 | 24.8(25.3) | 17.0 | 0.2(21.4) | -1.9 | 15.6(14.5) | 12.8 |
| | 7 | 317 | 23.0(22.5) | 16.0 | -2.7(21.3) | -6.4 | 15.7(14.6) | 12.5 |
| | 10 | 434 | 20.9(25.1) | 15.5 | -0.6(32.7) | -6.6 | 20.9(25.1) | 15.5 |
| P-value | | | 0.03 | | 0.002 | | 0.002 | |

*** Calculated as absolute value of (Sensor – YSI); where, for each paired point, SMBG = self-monitored blood glucose value, and Sensor = time-matched continuously measured glucose value

** Calculated as [(Sensor – YSI)/YSI]

* Calculated as the absolute value of [(Sensor – YSI)/YSI]

† Day from the time of sensor insertion (in 24-hour increments)

P-value is calculated on the chi-squared Kruskal-Wallis test form median.

ψ Percent of Points within 20% of Reference = 70.8, Percent of Points within 30% of Reference = 87.6

χ Percent of Points within 20% of Reference = 73.4 , Percent of Points within 30% of Reference = 88.7