A Pilot Trial in Pediatrics with the Sensor-Augmented Pump: Combining Real-Time Continuous Glucose Monitoring with the Insulin Pump

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Real-time continuous glucose monitoring and the insulin pump have been combined into the Sensor-Augmented Pump system (Medtronic MiniMed, Northridge, CA). This short-term pilot trial demonstrated that pediatric subjects with type I diabetes improved mean hemoglobin A1c (A1c) and glucose levels and reduced hypoglycemia and hyperglycemia using the Sensor-Augmented Pump system. ***(J Pediatr 2007;150:103-5)***

Two decades after the Diabetes Control and Complications Trial demonstrated the long-term benefits of lowering A1c levels,[1] only 30% of pediatric patients are able to achieve an A1c level <8.0%.[2-3] Recently, the Continuous Glucose Monitoring system (CGMS, Medtronic MiniMed, Northridge, CA) was shown to improve glycemic control in pediatric type I diabetes patients despite the fact that it only allows for retrospective review of the patient's glycemic patterns.[4-7] The purpose of the present pilot study was to determine if the Sensor-Augmented Pump could be used by pediatric patients with type I diabetes and whether using the real-time glucose values, glucose trend data, and hypoglycemic and hyperglycemic alerts improved glycemia and reduced episodes of hypoglycemia and hyperglycemia over time.

METHODS

Ten children, median age of 14.5 (mean 14.1 ± 2.6) years and mean diabetes duration 9.1 ± 3.3 years, were studied with the Sensor-Augmented Pump system (Figure). Subjects were followed at Childrens Hospital Los Angeles and used an insulin pump for >1 year. This study was approved by the hospital's Institutional Review Board; informed consent and assent were obtained from parents/patients.

Patients had four research visits at weekly intervals, wore seven subcutaneous glucose sensors for an average of 3 days each, and did four finger-stick blood glucose levels/day. Visit 1 included an overview of the Sensor-Augmented Pump: how to insert the sensor and affix transmitter, use of hypoglycemia and hyperglycemia alerts and glucose trend data, and obtaining an A1c using the DCA 2000 (Bayer, Tarrytown, NY). Visits 2, 3, and 4 involved downloading of sensor data, checking sensor sites, documenting sensor use, reviewing event diary and adverse events, making changes in the diabetes regimen, reviewing changes made by patients/families between visits, and distributing new supplies. A repeat A1c was done at visit 4.

Descriptive statistical analysis was performed for A1c values at baseline and end-of-study and treatment changes. Mean glucose values were compared looking at the time period during which subjects wore sensors 1 and 2 (the first 144 hours extracted from data summary tables) and the equivalent time period when sensors 6 and 7 were worn. Additional analysis occurred for the time period sensors 1,3, 5, and 7 were worn, standardized for 72 hours. Blocks of 5 minutes of hypoglycemia <50 mg/dL and hyperglycemia >250 mg/dL were identified per sensor.

RESULTS

The data yielded 202 days of user device experience. The mean A1c was 8.1% ± 0.9% at baseline and 7.8% ± 0.9% at study end. The Table (available at www.

A1c	Hemoglobin A1c	CGMS	Continuous Glucose Monitoring system

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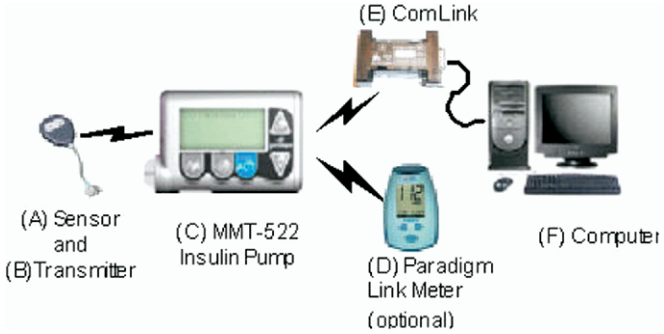

Figure. Sensor Augmented Pump System. Available in color at www.jpeds.com.

jpeds.com) shows that 7 of the 10 subjects had a decrease in A1c value. The mean glucose value for all subjects was 167 ± 19 mg/dL during sensors 1 and 2 and 155 ± 22 mg/dL for sensors 6 and 7. The Table also shows mean glucose values for each patient for sensors 1, 3, 5 and 7. Subjects mean glucose levels increased initially as they adjusted to the device but then decreased to below baseline values by sensor 7.

Hypoglycemia was experienced by 9 of the 10 patients throughout sensors 1, 3, 5, and 7 (Table). None met the definition of severe hypoglycemia. The mean number of 5-minute blocks of hypoglycemia was reduced from 9.4 ± 21.7 for sensor 1 to 5.3 ± 15.1 for sensor 7 per patient. All patients experienced hyperglycemia. The mean number of 5-minute blocks of hyperglycemia decreased from 64.9 ± 36.8 for sensor 1 to 44.7 ± 38.4 for sensor 7. Nine of the 10 patients showed a reduction in the number of blocks of hyperglycemia; there were no episodes of ketoacidosis.

There were a mean of 3.2 changes per patient in the treatment regimen. Of all changes made, 42% were made by increasing one or more basal rates on the insulin pump, 15% involved decreasing one or more basal rates, 30% increased the insulin-to-carbohydrate dose, 9% increased the amount of insulin given in the correction algorithm, and 4% altered the regimen for exercise.

DISCUSSION

The results of this pilot study indicate that pediatric subjects with type I diabetes were able to use the Sensor-Augmented Pump system to improve glycemia over a short time period. The system allowed for access to real-time glucose values, trend data, and hypoglycemic and hyperglycemic alerts so that patients/parents, with the aid of the diabetes team, could adjust insulin doses, energy intake, and activity pattern to decrease mean glucose and A1c levels, and to reduce hypoglycemia and hyperglycemia episodes.

Previous studies performed in pediatric subjects have shown that retrospective information obtained by the CGMS could be used to analyze glucose data, decrease A1c, reduce hypoglycemia, and give patients additional insight into their specific diabetes management issues.[4-11] Some studies have allowed patients to use the CGMS multiple times so that alterations in the regimen could be made and modified on repeated occasions.[10] Prior studies in children by Chase et al[8] and Kaufman et al[4] showed that using the CGMS led to a mean decrease in A1c of 0.2% to 0.3% over a 3-month time period, similar to the reduction over 1 month in the present study using real-time glucose values.

Our patients wearing the Sensor-Augmented Pump with access to real-time glucose values did not become overwhelmed or confused by the quantity of glucose data, or give inappropriate insulin doses. Rather, after a 3-hour education session and with weekly meetings with the research team, parents/patients were able to respond to the glycemic alerts and use the glucose trend data to make changes in the diabetes regimen to increase the number of glucose values in the target range. The most common changes in the regimen involved increasing one or another basal rates and bolus doses for food intake. It is possible that some of the improvement in glycemia was because of weekly meetings with the research team. To determine the contribution of the Sensor-Augmented Pump, randomized trials will need to be performed in the future.

This pilot study suggests that systems that provide continuous real-time glucose sensing with an insulin pump might enable more children with type I diabetes to avert the long-term and short-term complications of this disease that relate to abnormalities of glycemia.

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Fifty Years Ago in *The Journal of Pediatrics*

A LONG-TERM EVALUATION OF THE JUVENILE DIABETIC

Joos T and Johnston J. J Pediatr 1957;50:133-7

In the 1950s, children with diabetes mellitus were treated with NPH insulin alone or mixed with regular insulin, and diabetes control was determined by the Benedict reaction for urine glucose and determination of the number of times the patient was in a coma. For many years, patient measurement of urine glucose was the sole means of measuring metabolic control. In 1976, Malone et al provided evidence that urine glucose did not accurately reflect blood glucose (BG) concentrations.[1] In 1978, home BG monitoring became widely available, and now a patient can measure BG levels at home in 5 seconds with 1 μL of blood. In 1978, Bunn et al reported the relevance of glycosylated hemoglobin to long-term metabolic control in type 1 diabetes mellitus, further improving our ability to monitor glycemia.[2]

In 1957, Joos and Johnston noted that patients with good control had fewer complications, recommending children be placed on rigid diets and be allowed to spill 2+ urine glucose to avoid hypoglycemia. In this, they were prescient, because the controversy about whether "tight" control resulted in fewer microvascular complications raged until the Diabetes Control and Complications Trial (DCCT) in 1987 stopped the arguments.[3]

Since the publication of this paper, the understanding and management of type 1 diabetes mellitus has improved dramatically. After the DCCT, newer insulins were developed and insulin pump technology expanded, both of which more closely mimic physiologic insulin secretion. Frequent home glucose monitoring has shown to predict good glycemia as determined by HbA1c levels,[4] and nutrition recommendations have liberalized. The 1957 article recommended diets based on age, growth, and pubertal status. The authors state "the caloric distribution of the mixture should be kept constant, deriving 16% from protein, 50% from fat, and 35% from carbohydrate," to maintain glycemic control with a fixed insulin dose. This constant intake was necessary to maintain glycemic control in patients taking a fixed insulin dose. The rapid-acting analogues have allowed for the return to the "free diet" that the authors recommended against. Patients can now dose their insulin on the basis of the food they eat, rather than having to eat to cover their insulin. Newer insulins allow more flexibility in lifestyle, but require more attention to food intake and BG monitoring.

The frequency of complications has also changed; in the 1957 report, 59% of the 44 patients with diabetes mellitus >10 years in duration had vascular complications: 41% had retinopathy, 16% had isolated microalbuminuria, and 11% had nephropathy. In children with a mean diabetes mellitus duration of 6.8 years, 20% had retinopathy and 6% had microalbuminuria.[5]

With advances in diabetes mellitus management in the past half century, complication rates and normalization of lifestyle have improved. Recent advances with continuous BG monitoring, using a subcutaneously inserted sensor and insulin pump technology, have begun to "close the loop." Future therapies such as implantable insulin pumps, islet stem cell therapy, and even beta cell regeneration excite us about the 50 years to come.

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Table. A1c, daily glucose levels, mean glucose by sensor, and number of hypoglycemia (values <50 mg/dL) and hyperglycemia (values >250 mg/dL) episodes by sensor

Patient	1	2	3	4	5	6	7	8	9	10	All
A1c % start	7.0	6.9	9.4	7.5	7.0	8.3	9.3	8.8	8.2	8.3	8.1±0.9
A1c % end	7.3	6.7	8.7	7.3	6.7	7.7	9.4	7.7	8.2	8.2	7.8±0.9
Mean daily glucose mg/dL Sensor 1-2 (1st week)	194±55	143±34	187±23	154±14	153±23	175±24	183±21	138±21	171±31	174±46	167.2±19
Mean daily glucose mg/dL Sensor 6-7 (last week)	182±26	120±21	172±22	163±38	145±38	138±28	167±24	123±25	177±20	169±31	155.6±22
Mean glucose mg/dL Sensor 1	176.7	124.3	220.4	142.6	146.5	155.1	173.5	138.6	168.4	150.0	159.4
Mean glucose mg/dL Sensor 3	167.8	123.8	180.6	141.6	156.8	142.5	188.7	154.6	216.1	181.2	165.4
Mean glucose mg/dL Sensor 5	155.0	117.0	172.0	164.2	155.0	122.6	170.7	123.8	211.6	187.0	157.9
Mean glucose mg/dL Sensor 7	180.1	123.5	168.1	138.3	138.3	145.7	164.5	112.4	160.1	147.4	147.5
Hypoglycemia # Sensor 1	0	70	6	0	5	1	0	12	0	0	9.4
Hypoglycemia # Sensor 3	0	68	6	38	0	0	1	37	0	0	15.0
Hypoglycemia # Sensor 5	9	61	0	0	0	6	0	10	2	0	8.8
Hypoglycemia # Sensor 7	4	48	1	0	0	0	0	0	0	0	5.3
Hyperglycemia # Sensor 1	82	55	60	57	21	71	119	11	125	48	64.9
Hyperglycemia # Sensor 3	98	27	26	64	51	18	151	146	287	154	102.2
Hyperglycemia # Sensor 5	131	63	85	137	45	13	73	11	275	158	99.1
Hyperglycemia # Sensor 7	118	18	65	19	19	16	74	8	22	88	44.7