

Use of Insulin Pump Therapy at Nighttime Only for Children 7–10 Years of Age With Type 1 Diabetes

FRANCINE RATNER KAUFMAN, MD
MARY HALVORSON, MSN, CDE

CHRISTINA KIM
PISIT PITUKCHEEWANONT, MD

OBJECTIVE — Because of age-related developmental and cognitive issues, children <10 years of age may not be able to wear an insulin pump safely when they are not under direct parental supervision. The purpose of this study was to determine if insulin pump therapy at nighttime only, when children are at home, could improve fasting and nighttime blood glucose levels without adverse effects.

RESEARCH DESIGN AND METHODS — The study cohort consisted of 10 children aged 7–10 years. A randomized crossover design was used to compare nighttime-only pump usage from dinner and throughout the night, combined with a prebreakfast injection of intermediate-acting NPH and rapid-acting lispro insulin, with 3 insulin injections per day. Comparisons were made among mean blood glucose values and percentage of blood glucose levels within the target range (70–150 mg/dl) before meals, at bedtime, and at 3:00 A.M.; serum fructosamine levels; and scores on measures of adherence and fear of hypoglycemia.

RESULTS — Compared with baseline levels, the use of the pump resulted in a significant decrease in the mean average ($P < 0.001$), breakfast ($P < 0.0001$), and 3:00 A.M. ($P < 0.003$) blood glucose levels. There was a decrease in the percentage of blood glucose values less than the target range ($P < 0.01$) and in fructosamine ($P < 0.01$) values and an increase in the percentage of blood glucose levels within the target range ($P < 0.03$).

CONCLUSIONS — Nighttime-only insulin pump therapy may be a viable alternative that young children can use to improve glycemia when they are not capable of independently managing an insulin pump.

Diabetes Care 23:579–582, 2000

Since the introduction of continuous subcutaneous insulin infusion (CSII) in the late 1970s, it has become apparent that the use of insulin pump therapy to treat type 1 diabetes has many potential benefits (1–6). CSII may be a more physiological way to deliver insulin, and numerous studies have shown that it can improve glycemia (7–10). However, as

with any advanced medical technology, to minimize risk and maximize benefit, patients who wear an insulin pump must have sufficient knowledge and skills and the appropriate attitude to use CSII successfully (11). Subjects must be able to wear and protect the pump, to deliver bolus and basal insulin dosages, and to suspend insulin delivery if indicated.

In pediatrics, insulin pump therapy may be limited. Because of many developmental and cognitive issues, young children <10 years of age may not be able to wear the insulin pump safely when they are in school and not under direct parental supervision or in the care of another adult willing to assume responsibility for their diabetes care. As a result, we began to investigate whether there were alternative ways to use CSII in young pediatric subjects while ensuring safety.

The purpose of the present study was to determine if the use of the insulin pump at nighttime only could improve glycemia in young children with type 1 diabetes. Because children <10 years of age are at home and in the care of their parents at night, we hypothesized that these children could use an insulin pump during the night to improve nighttime and fasting blood glucose levels without increasing hypoglycemia.

RESEARCH DESIGN AND METHODS

Study population

The study population consisted of 10 children <10 years of age who had a history of nighttime hypoglycemia and/or hyperglycemia. The mean age of the subjects was 9.2 ± 1.1 years; the mean duration of diabetes was 3.4 ± 1.6 years; the mean insulin dosage was $0.9 \pm 0.3 \text{ U} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ (distributed as ~60–70% in the morning [25–30% rapid-acting and 70–75% intermediate-acting insulin], 15–20% rapid-acting at dinner, and 15–20% intermediate-acting insulin at bedtime); the mean HbA_{1c} value was $7.6 \pm 0.9\%$ (range 6.4–9.4%).

Study protocol

As shown in Fig. 1, the study was a randomized crossover design that included treatment with a MiniMed 507C insulin pump (MiniMed, Sylmar, CA) containing rapid-acting lispro insulin (Humalog; Eli Lilly, Indianapolis, IN) during the nighttime only. The insulin dosage was determined by decreasing by 20% the average total insulin dosage per day over the preceding 3 days. The basal infusion rate was calculated to be

From the Department of Pediatrics (F.R.K., M.H., C.K., P.P.), University of Southern California School of Medicine; and the Division of Endocrinology and Metabolism (F.R.K., M.H., C.K., P.P.), Childrens Hospital Los Angeles, Los Angeles, California.

Address correspondence and reprint requests to Francine R. Kaufman, MD, 4650 Sunset Blvd., Los Angeles, CA 90027. E-mail: fkaufman@chla.usc.edu.

Received for publication 4 October 1999 and accepted in revised form 15 December 1999.

F.R.K. and M.H. have received grants, consulted for, and are stockholders in MiniMed.

Abbreviations: CSII, continuous subcutaneous insulin infusion.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

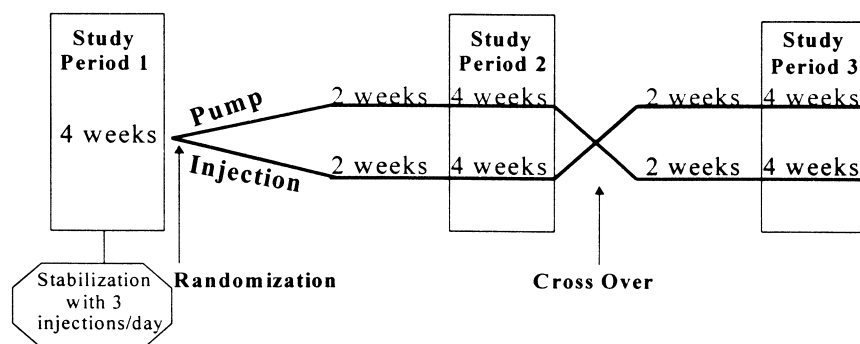


Figure 1—Study protocol.

50% of the total dosage; 60% converted to NPH got the A.M.-to-dinner coverage and 40% as the basal rate for the pump to cover from dinner to morning. The remaining 50% of the total dosage was changed to rapid-acting insulin using 0.5 U insulin per 15 g of carbohydrate for meals and snacks. The dinner and bedtime snack boluses were given with the use of the pump; for every 15 g of carbohydrates consumed with dinner and the bedtime snack, 0.5 U insulin was administered. The prebreakfast rapid-acting lispro insulin was delivered by use of the pump or was mixed with the intermediate-acting NPH insulin, which was administered with the use of a syringe before the catheter was disconnected for the day. The pump catheter was left in place for 3 days; the pump was disconnected during the day and remained at home. Reconnection of the pump occurred for the dinner bolus of insulin. This regimen was compared with 3 injections per day of lispro and NPH before breakfast, lispro before dinner, and NPH before bedtime. Additional insulin for correction of blood glucose levels >150 mg/dl was given in both groups before meals and bedtime by using a correction dosage of 0.5 U for every 50 mg/dl that the blood glucose level was >150 mg/dl.

After informed consent was obtained, there was a 4-week stabilization period (period 1) for all subjects, during which 3 injections of insulin were given per day. Half of the subjects were then randomly assigned to begin therapy with the insulin pump, and the remainder continued therapy with insulin injections. After a 2-week stabilization period, during which insulin dosage adjustment for both groups was performed by 1 individual, the first study period began and lasted 4 weeks (period 2). At the end of this period, subjects were crossed over, and the protocol was repeated

(period 3). During the dosage-adjustment period, 8 of 10 subjects, while on the insulin pump, required an increase in the basal infusion rate by 0.1–0.2 U/h from dinner until midnight.

Blood glucose levels were obtained by finger-stick measurements (One Touch Profile; LifeScan, Milpitas, CA) before meals (breakfast, lunch, and dinner), at bedtime, and at 3:00 A.M. Comparisons were made between the mean values at these times and the mean average blood glucose level. In addition, the mean percentage of blood glucose levels within, greater than, and less than the target range of 70–150 mg/dl was evaluated. Comparisons were made between period 1 and periods 2 and 3 combined, during which injections were given, and periods 2 and 3 combined, during which the insulin pump was used. In addition, comparisons were made between the mean serum fructosamine (normal range <250 $\mu\text{mol/l}$) (Endocrine Science Laboratory, Tarzana, CA) values obtained at these times. Mean HbA_{1c} levels (DCA 2000; Bayer, Tarrytown, NY), mean insulin dosage per kilogram, mean scores on measures of adherence (12) and the fear of hypoglycemia (13), and mean BMI were compared between period 1 and the periods during which the insulin pump was used. Statistical analysis was done by paired and unpaired *t* tests.

RESULTS — The results of this study are given in Table 1. There were no differences in the mean average; premeal (breakfast, lunch, and dinner), bedtime, and 3:00 A.M. blood glucose levels; the percentage of blood glucose levels within, greater than, and less than the target range; and the mean fructosamine values at the end of the pump periods compared with those at the end of period 1. In addition, there was a

significant increase in the percentage of blood glucose levels within the target range and a significant decrease in the percentage of blood glucose levels less than the target range at the end of the pump periods compared with those at the end of period 1. These results were in contrast to what was seen for the time periods during which the insulin pump was used. As shown, there was a significant decrease in the mean average, breakfast, and 3:00 A.M. blood glucose levels and the mean fructosamine values during the pump periods compared with those during period 1.

Table 1 shows also the comparison of the combined insulin injection groups with the combined insulin pump groups from periods 2 and 3. As shown, there was a significant decrease in the mean average, breakfast, and bedtime blood glucose levels and mean fructosamine values, and there was an increase in the percentage of blood glucose values within the target range for the pump groups, as compared with those of the injection groups. There was no difference in blood glucose results when use of the pump in period 2 was compared with use of the pump in period 3.

Results on the adherence and fear of hypoglycemia measures after the periods of using the pump showed that, as compared with the scores during period 1, there was a significant increase in the scores on adherence (77 ± 11 vs. 86 ± 6 , $P < 0.04$) and a decrease in the fear of hypoglycemia (27 ± 15 vs. 12 ± 9 , $P < 0.02$). Similarly, there was a decrease in the mean total insulin dosage (0.9 ± 0.3 vs. 0.7 ± 0.2 U \cdot $\text{kg}^{-1} \cdot \text{day}^{-1}$, $P < 0.05$) after the insulin pump periods. However, there was no change in BMI (18.9 ± 1.9 vs. 18.7 ± 2.4) or the mean HbA_{1c} values (7.6 ± 0.9 vs. $7.5 \pm 0.6\%$). During the study, there were no apparent catheter occlusions.

CONCLUSIONS — These data reveal that use of the insulin pump at nighttime only had benefits for young children with type 1 diabetes. Despite the small sample size and limited duration of this study, it appears that nighttime use of the pump improved glycemia, as evidenced by decreased fructosamine values. After connecting the pump and taking the dinner bolus of insulin matched to the carbohydrate intake of the meal, blood glucose levels before bedtime, at 3:00 A.M., and in the morning before breakfast were more often in the target range. This improvement was accomplished with less hypoglycemia and

a reduction in overall insulin dosage. It was also associated with improved adherence with the diabetes regimen and improved quality of life due to a diminished fear of hypoglycemia. As expected, there were no differences in lunch and dinner blood glucose levels with the pump compared with those with injections; using the pump at nighttime only does not appear to affect those time periods.

Insulin pump therapy has been documented to lead to improved glycemia in a variety of clinical conditions. It appears to benefit pregnant women (4,14) and difficult-to-manage patients (15,16). Moreover, it has reduced retinopathy (17,18), hyperlipidemia (19,20), and hypoglycemia unawareness (6) in adult type 1 subjects. In adolescents and older children, it has been shown to ameliorate the recurrent diabetic ketoacidosis (9) and the growth delay (5) associated with poor diabetes control. As recently reported by Boland et al. (21), the insulin pump has been shown to be a superior modality compared with multiple injection therapy for adolescents attempting to achieve the intensive type of outcome seen in the Diabetes Control and Complication Trial (22). In the study by Boland et al. (21), adolescents who chose insulin pump therapy were able to maintain an HbA_{1c} level of 7.5% at the end of a 12-month time period. Not only did these subjects improve glycemia and therefore reduce their risk of long-term complications, but they experienced a significant reduction in the rate of severe hypoglycemia.

However, few studies conducted with CSII have focused on preteen and younger children. It is unclear whether CSII is as beneficial in young children, because young children may not have the skills, the cognitive development, and the maturity to use CSII safely and successfully. There is a concern that CSII may not be able to be managed when children are at school and not under the direct supervision of their parents. This concern has led to the unwillingness of health care providers to recommend the insulin pump for preteen children.

According to Wysocki et al. (23,24), children 7–10 years of age are just beginning to master some of the technical tasks and are beginning to gain some of the cognitive skills required for diabetes management. These children can learn to administer insulin, although they cannot prepare the syringe. They can understand some aspects of the nutritional plan, although they cannot comprehend carbo-

Table 1—The mean blood glucose level (mg/dl); the percentage of blood glucose levels within, greater than, and less than the target range; and the fructosamine levels (μmol/l)

	4-Week values			P	
	Baseline	Injection	Pump	Baseline vs. pump	Pump vs. injection
Average BG level	186 ± 31.9	181 ± 33.6	160 ± 19.6	0.001	—
Breakfast BG level	197 ± 31.2	185 ± 35.2	125 ± 31.3	0.0001	0.001
Lunch BG level	137 ± 38.7	146 ± 38.8	157 ± 38.6	—	—
Dinner BG level	191 ± 53.7	191 ± 54.5	183 ± 42.1	—	—
Bed BG level	141 ± 3.7	156 ± 28.1	118 ± 14.0	—	0.003
3:00 A.M. BG level	173 ± 48.8	178 ± 46.1	132 ± 25.2	0.003	0.02
% BG levels in target	36 ± 7.5	37 ± 6.7	44 ± 6.7	0.03	0.04
% BG levels > target	43 ± 12.7	43 ± 11.8	41 ± 10.6	—	—
% BG levels < target	21 ± 10.0	20 ± 9.1	15 ± 6.3	0.01	—
Fructosamine levels	386 ± 56*	390 ± 45.5*	345 ± 36.6	0.01	0.03

Data are means ± SD. BG, blood glucose. *NS.

hydrate management or counting. Although they understand that high blood glucose levels require a correction dosage of insulin, they are not consistently able to determine the quantity of that correction dosage. These children may know that exercise has an effect on blood glucose levels; however, they do not know how to adjust their insulin regimen to counterbalance the impact of planned or unplanned activities on diabetes control. Therefore, these young school-aged children, although they have emerging skills and knowledge, still require supervision.

While children are in school and away from their parents, little is required of them if they are on insulin-injection therapy. They have taken their morning injection at home, and, for the most part, they do not need to take additional insulin while they are in school. The only procedure they are required to perform is a finger-stick blood glucose determination, which markedly contrasts what is required if they are to wear an insulin pump. Because the pump catheter can become dislodged and the pump can stop functioning, those who wear an insulin pump must be prepared at all times to reinsert the infusion catheter or trouble-shoot complications with insulin delivery. They must have the cognitive ability to calculate the dosage of insulin required for lunch, to take into account how to correct for an abnormal blood glucose value, and to accordingly adjust the bolus for the meal. They must also know what to do for planned and unplanned activities and when to suspend insulin delivery if indicated. Most importantly, they need to have the appropriate attitude to

protect the pump and to feel safe wearing it, and they must be psychologically prepared to deal with using it.

Children 7–10 years of age often do not possess all of the aforementioned qualities that would enable them to use CSII throughout the entire day, particularly when they are in school. After Schiffman and Belmonte (25) and Kanc et al. (26) suggested that the insulin pump could be used intermittently in conjunction with insulin-injection therapy, this study was designed to determine if nighttime pump use in young children could be beneficial and safe. The results indicate that nighttime pump use, when young children are home and under the supervision of their parents, is a viable alternative to continuous pump therapy. Nighttime pump use enables them to benefit from CSII, with regard to improving glycemia and reducing hypoglycemia, before they are capable of independently managing an insulin pump.

Acknowledgments

This study was supported in part by a National Institutes of Health NCCR GCRC Grant (MO1 RR-43) and was conducted at the GCRC at Childrens Hospital Los Angeles.

References

1. Saudek CD: Novel forms of insulin delivery. In *Endocrinology and Metabolism Clinics of North America: Current Therapies for Diabetes*. Vol. 26. Hirsch IB, Riddle MC, Eds. Philadelphia, WB Saunders, 1997, p. 599–610
2. Tamborlane WV, Sherwin RS, Genel M, Felig P: Reduction to normal plasma glucose in juvenile diabetes by subcutaneous administration of insulin with a portable

- infusion pump. *N Engl J Med* 300:573–578, 1979
3. Tamborlane WV, Sherwin RS, Genel M, Felig P: Outpatient treatment of juvenile-onset diabetes with a preprogrammed portable subcutaneous insulin infusion system. *Am J Med* 68:190–196, 1980
4. Hirsch IB: Intensive treatment of type 1 diabetes. In *Medical Clinics of North America: Prevention and Treatment of Diabetes and Its Complications*. Vol. 82. Skyler JS, Ed. Philadelphia, WB Saunders, 1998, p. 689–720
5. Rudolf MC, Sherwin RS, Markowitz R, Bates SE, Genel M, Hochstadt J, Tamborlane WV: Effect of intensive insulin treatment on linear growth in the young diabetic patient. *J Pediatr* 101:333–339, 1982
6. Farkas-Hirsch R, Hirsch IB: Continuous subcutaneous insulin infusion: a review of the past and its implementation for the future. *Diabetes Spectrum* 7:80–84, 1994
7. Mecklenburg RS, Benson EA, Benson JW Jr, Bloomenstein EA, Fredlund PN, Guinn TS, Metz RJ, Nielsen RL: Long-term metabolic control with insulin pump therapy: report of experience with 127 patients. *N Engl J Med* 313:465–468, 1985
8. Bending JJ, Pickup JC, Keen H: Frequency of diabetic ketoacidosis and hypoglycemic coma during treatment with continuous subcutaneous insulin infusion: audit of medical care. *Am J Med* 79:685–691, 1985
9. Steindel BS, Roe TF, Costin G, Carlson M, Kaufman FR: Continuous subcutaneous insulin infusion (CSII) in children and adolescents with chronic poorly controlled type 1 diabetes mellitus. *Diabetes Res Clin Pract* 27:199–204, 1995
10. Oesterle A, Boland E, Yu C, Tamborlane W, Grey M: CSII: A “new” way to achieve strict control and lower the risk of severe hypoglycemia in adolescents (Abstract). *Diabetes* 47 (Suppl. 1):A342, 1998
11. Kaufman FR, Halvorson M, Miller D, Mackensie M, Fisher LK, Pitukcheewanont P: Insulin pump therapy in type 1 pediatric patients: now and into the year 2000. *Diabetes Metab Res Rev* 15:338–352, 1999
12. Israel C, Berndt DJ, Barglow P: Development of a self-report measure of adherence for children and adolescents with insulin-dependent diabetes. *J Youth Adolescence* 15: 419–428, 1986
13. Irvine A, Cox D, Gonder-Frederick L: The fear of hypoglycemia scale. In *Measurement Tools in Patient Education*. Redman BK, Ed. New York, Springer, 1998, p. 133–155
14. Coustan DR, Reece EA, Sherwin RS, Rudolf MC, Bates SE, Sockin SM, Holford T, Tamborlane WV: A randomized clinical trial of insulin pump vs. intensive conventional therapy in diabetic pregnancies. *JAMA* 255: 631–636, 1986
15. Blackett PR: Insulin pump treatment for recurrent ketoacidosis in adolescence. *Diabetes Care* 18:881–882, 1995
16. Turbiana-Rufi N, de Lonlay P, Bloch J, Czer-nichow P: Remission of severe hypoglycemia incidents in young diabetic children treated with subcutaneous infusion. *Arch Pediatr* 3:969–976, 1996
17. White NH, Waltman SR, Krupin T, Santiago JV: Reversal of abnormalities in ocular fluorophotometry in insulin-dependent diabetes after five to nine months of improved metabolic control. *Diabetes* 31: 80–85, 1982
18. Selam JL, Millet P, Zaluski S, Saeidi S, Mirouze J: Beneficial effect of glycaemic improvement in non-ischaemic forms of diabetic retinopathy: a 3-year follow-up. *Diabet Med* 3:60–64, 1986
19. Falko JM, O’Dorisio TM, Cataland S: Improvement of high-density lipoprotein-cholesterol levels: ambulatory type 1 diabetics treated with the subcutaneous insulin pump. *JAMA* 247:37–39, 1982
20. Pietri AO, Dunn F, Grundy SM, Raskin P: The effect of continuous subcutaneous insulin infusion on very low-density lipoprotein triglyceride metabolism in type 1 diabetes mellitus. *Diabetes* 32:75–81, 1983
21. Boland EA, Grey M, Oesterle A, Frederickson 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* 22:1779–1784, 1999
22. The Diabetes Control and Complications Trial Research Group: The absence of a glycemic threshold for the development of long-term complications: the perspective of the Diabetes Control and Complications Trial. *Diabetes* 45:1289–1298, 1996
23. Wysocki T, Wayne W: Childhood diabetes and the family. *Practical Diabetology* 31 June 1992
24. Wysocki T, Taylor A, Hough BS, Linscheid TR, Yeates KO, Naglieri JA: Deviation from developmentally appropriate self-care autonomy: association with diabetes outcomes. *Diabetes Care* 19:119–125, 1996
25. Schiffrin A, Belmonte M: Combined continuous subcutaneous insulin infusion and multiple subcutaneous injections in type 1 diabetic patients. *Diabetes Care* 4:595–600, 1981
26. Kanc K, Janssen MMJ, Keulen ET, Jacobs MA, Popp-Snijders C, Snoek FJ, Heine RJ: Substitution of night-time continuous subcutaneous insulin infusion therapy for bedtime NPH insulin in a multiple injection regimen improves counterregulatory hormonal responses and warning symptoms of hypoglycemia in IDDM. *Diabetologia* 41: 322–329, 1998