Int J Diabetes & Metabolism (2008) 16: 57-61

Insulin Pump Therapy in Type 1 Diabetic Patients: Experience at the American University of Beirut Medical Center

M Merheb, J Chaiban, I Salti, R Sammak, M Choucair, M Nasrallah,
Division of Endocrinology, Department of Medicine, American University of Beirut Medical Center, Beirut, Lebanon

Abstract
Objective: To study glycemic control after initiation of pump therapy in a group of patients with type 1 diabetes..**Materials and Methods**: We reviewed all consecutive charts of adolescent and adult Lebanese patients with type 1 diabetes treated at the American University of Beirut Medical Center who were started on continuous subcutaneous insulin infusion (CSII) between 2003 and 2005. Their previous insulin regimen included premixed insulin preparation, glargine/lispro or NPH with short-acting insulin, as 2 or 3 injections per day. **Results:** The charts of 12 patients (7 men and 5 women) were reviewed. Their median age was 24.5 years (range 16-45) and the median disease duration was 10 years (range 2-21). At the time of study, the median duration of pump use was 18 months (range 2-28). Hemoglobin A1C significantly improved [median 8.4 (6.5-10) to 6.9 (5-8.5) % , p=0.003] and the rate of hypoglycemia was reduced (from a total of 32 to 4 episodes per week), with no significant effects on body weight or insulin dose. While on CSII, all patients reported satisfaction in their quality of life in terms of physical, emotional and social well-being. **Conclusion:** This case series is the first to report the use and outcome of CSII in Lebanon with improved glycemic profile and quality of life in adult patients with type 1 diabetes.

Keywords: *Type 1 Diabetes; insulin pump; continuous subcutaneous insulin infusion; Lebanon; Middle East.*

Introduction

In 1993, The Diabetes Control and Complications Trial (DCCT) demonstrated that tight glycemic control in young adults with type 1 diabetes reduced the incidence of microvascular complications.[1,2] The benefits of this intense control was maintained even when HbA1c did not remain in the tight range after the DCCT was over, as was demonstrated in the EPIC study which is a follow-up on the DCCT population.[3] The EPIC study also demonstrated more recently that the benefits of tight glycemic control extend to prevention of macrovascular complications.

Since its first use in the 1970s by Pickup et al. in UK, [4,5] overwhelming evidence supports the effectiveness of Continuous Subcutaneous Insulin Infusion (CSII) also known as "insulin pump therapy" to achieve better metabolic control in patients with type 1[6-9] and type 2[10-12] diabetes who have failed to achieve their targets on multiple daily insulin injections (MDI). The overall decrease in HbA1c which is attributed to CSII is 0.35%, among various study groups, with less hypoglycemic episodes.

Since its publication, the DCCT has inspired the initiation of several clinical trials to assess this intensive therapy, through non-randomized studies including children and adolescents using at that time regular insulin for the pump.[13-15] In fact in the 'intense glucose control' arm of the DCCT, 42% of patients were using insulin pump therapy at the end of the study and were able to maintain a mean HbA1c of 6.8 % vs. 7.0% in MDI-treated subjects ($p<0.05$).[16]

The implementation of the insulin pump therapy mandates a lot of input and motivation on behalf of the patient in coordination with a highly skilled multidisciplinary team. Cultural diversity and social support systems may play a role in the success rate of this technology. Socioeconomic status, more so than race/ethnicity, plays an important role in metabolic control.[17] There are no reports of pump use among Middle East adult patients with type1 diabetes. Given that the culture and social background of these patients may be different from those in previously published insulin pump studies, we have asked whether the benefits of this new technology are seen across our population as well. We have conducted this study to assess the outcome in Lebanese type 1 diabetic patients who were placed on Continuous Subcutaneous Insulin Infusion at the American University of Beirut.

Materials and Methods

All consecutive Lebanese patients who were started on the pump since its introduction to our institution in May 2003 until September 2005 (the time of the study) were included. All patients were using Medtronic/Minimed Pump.

Received on: 24/12/2007
Accepted on: 20/07/2008

Correspondence to: Mona Nasrallah, Division of Endocrinology and Metabolism Department of Internal Medicine PO Box: 11-0236/D23, Phone: +961 1 340 460 (extension 5366) ; Fax: + 961 1 380 714 ; E-mail: mn36@aub.edu.lb.

There were 12 patients: 7 men and 5 women. Their charts were reviewed and data was collected regarding the age of onset of diabetes, the date of initiation of insulin pump therapy, and the duration of pump therapy until study date, along with HbA1c and lipid profile values (when available) before and during therapy. HbA1c was determined using Bayer DCA 2000 Analyzer (Bayer Diagnostics, Inc, USA). When several values of HbA1c were available, the mean of all values was used for comparison.

Patients were performing self-monitoring blood glucose by fingerstick at least 3 times per day: fasting, postprandial and at bedtime. The mean fasting blood glucose and 2-hours postprandial were calculated for each patient separately.

Weight before and after pump use and the level of daily activity were recorded. The presence of macrovascular (coronary artery disease, peripheral artery disease or cerebrovascular disease) and microvascular complications (neuropathy, nephropathy and retinopathy) were based on the information in medical charts.

Patients were contacted by phone; if verbal consent was obtained, we then proceeded with the interview. Additional information was obtained regarding: the number of hypoglycemic episodes per week defined as a low blood glucose according to its severity (mild: 50-60 mg/dl, moderate: 30-50 mg/dl or severe : less than 30mg/dl), the occurrence of coma or seizure. Diabetic ketoacidosis (DKA) and any hospitalizations for complications of diabetes mellitus were also recorded.

Any adverse side effect believed to be related to the insulin pump use was documented during the interview, such as infection at site of injection, catheter blockage, or lipodystrophies.

Quality of life assessment was based on a 5-point Likert scale measurement for each one of the criteria: 1) physical/functional feeling of well-being, 2) emotional influence of such therapy, 3) impact of the pump on family relationships and attendance of social activities, 4) the overall treatment satisfaction scoring system was as follows: 1= dissatisfied and 5 = very satisfied.

Table 1. Baseline characteristics of patients

Patient	Age (years)	Sex M/F	Duration of disease (years)	Age at Initiation of Pump (years)	Duration of Pump use (months)
1	22	M	10	20	24
2	27	M	10	25	24
3	16	F	2	15.25	9
4	17	M	3	14.6	28
5	17	F	5	15	23
6	35	F	15	33.5	18
7	42	M	17	40.5	18
8	18	M	16	16.4	19
9	40	F	21	38.8	14
10	38	F	8	37	12
11	22	M	2	21.8	2
12	45	M	12	44.8	2
Median (*range*)	24.5 (16-45)	7/5	10 (2-28)	23.4 (14-44)	18 (2-28)

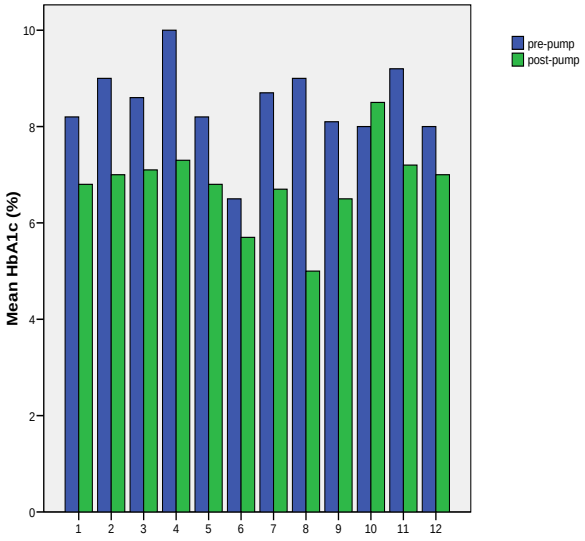

Figure 1: The mean of individual HbA1c values are represented for each patient, before and after pump use. All patients had a significant decrease in HbA1c after pump initiation, except for patient 10 (p=0.003).

This study was approved by the Institutional Research Board of the American University of Beirut and all procedures were in accordance with the Helsinski Declaration of 1975, as revised in 1983.

Statistical Analysis

All parameters are expressed as median (minimum and maximum), unless stated otherwise. The median of continuous variables (weight, HbA1c, insulin dose) before and after pump use were compared using Wilcoxon signed-rank test. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using the software SPSS 14.0 (SPSS Inc., Chicago, Illinois).

Results

Patient characteristics

All 12 patients were included in the analysis. There were 7 males and 5 females (Table 1), all with type 1 diabetes. All were followed up at the American University of Beirut Medical Center, Beirut, Lebanon. Close communication by frequent clinic visits, phone calls and 24 h direct accessibility to counseling by our Diabetes Nurse Educator, and medical care by one of three endocrinologists were assured to each patient. Patients received intensive education about the pump, how to trouble shoot, how to identify hypo/hyperglycemia, and what to do to correct the situation.

Their median age was 24.5 years (16-45), duration of disease 10 years (2-21 years), and the median age at pump initiation 23.4 years (14-44). Their previous insulin regimens were heterogeneous and included premixed

Table 2. Comparison of metabolic control before and after CSII use.

Patient	Weight (Kg)		Insulin (units/day)		FBS		Post-prandial BS (mg/dl)		HbA1c (%)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	75	80	95	90	300	92	400	190	8.2	6.8
2	77	82	50	50	135	90	200	180	9.0	7.0
3	34	49	03	*NA*	180	110	295	161	8.6	7.1
4	65	88	48	55	338	141	450	200	10.0	7.3
5	50	52	40	33	350	120	200	180	8.2	6.8
6	52	52	30	26	120	130	150	139	6.5	5.7
7	88	87	75	40	281	135	369	71	8.7	6.7
8	51	51	40	44	300	92	300	180	9.0	5.0
9	74	76	30	25	300	135	300	520	8.1	6.5
10	85	78	40	*NA*	361	85	300	200	8.0	8.5
11	56	60	22	*NA*	*NA*	140	*NA*	180	9.2	7.2
12	60	62	40	40	*NA*	100	*NA*	120	8.0	7.0
Median *(range)*	62 (43-88)	68 (49-88)	40 (22-95)	40 (25-90)	300 (120-361)	110* (85-141)	300 (150-450)	180* (30-205)	8.4 (6.5-10)	6.9* (5-8.5)
Mean ±SD	65±15	68±15	45±21	34±26	222±131	113±22	247±143	167±39	8.5±0.9	6.8±0.9

* = $p<0.05$

insulin preparation (70/30) given twice per day, glargine with multiple lispro injections, or NPH given once or twice per day with short-acting insulin injections at least 3 times per day.

The median duration of pump use was 18 months (2-28). Four patients started pump therapy before 18 years of age, at a median of 15.1 years (14-16).

Glycemic control

The median HbA_{1c} level before initiating pump therapy of all patients was 8.4 %(6.5-10) and decreased to 6.9% (5-8.5), P=0.003 (Figure 1). Eight out of 12 patients were able to lower their HbA1c to ≤7.0% (Table 2).

There was no difference regarding their weight when comparing pre- and post-pump periods [62 Kg (43-88) for pre, vs. 68 Kg (49-88) for post-pump period, p=0.061]. Although the insulin dose did not change [40 units/day (22-95) vs. 40 units/day (25-90), p=0.122], the insulin unit per kg per day decreased significantly from a pre-pump insulin dose of 0.68 units/kg/day (0.39-1.27) to a post-pump dose of 0.62 units/kg/day (0.33-1.13), p=0.013. The median fasting blood glucose was 300 mg/dl (120-361) pre- versus 110mg/dl (85-141), p=0.007 and post-prandial glucose was 300mg/dl (150-450) versus 180 mg/dl (30-205), p=0.005.

Patient 7 had type 1 diabetes for more than 15 years, and was pregnant at the end of her first trimester when she was started on CSII. Her HbA1c was uncontrolled prior to CSII and improved for the whole period of pregnancy and delivery with 6.5 and 5.7%, respectively. The baby boy was born healthy at 34 weeks gestation with a birth weight of 2800 g.

Adverse events

None of the patients reported infection at the site of catheter insertion.There were a total of 32 episodes of hypoglycemia per week (as per patient recollection) before the initiation of CSII, with 6 patients experiencing more than 2 episodes per week. The episodes decreased to 4 in total per week after CSII, with none of the patients experiencing more than 2 episodes. No one reported severe hypoglycemia leading to coma. There was no difference in DKA episodes, occurring in two patients pre-pump, and in one patient while on CSII. The latter event was related to kinking of the pump catheter. Their quality of life while on CSII was highly satisfactory at all levels of physical, emotional and social functioning as reflected by the Liekert additive mean score of 4.2 (± 0.6) out of 5.

Discussion

Continuous Subcutaneous Insulin Infusion or "insulin pump" technology has been available in Lebanon since 2003. Our small case series study confirms the advantages of this intensive insulin therapy and extends it to the Lebanese population with type 1 diabetes mellitus. Two thirds of our patients were able to achieve a HbA1c ≤ 7.0% with no reported deleterious effects on weight, the rate of hypoglycemic episodes, or DKA.

This benefit was seen across all subsets within our population. Thus, one third of our patients were adolescents at the time of pump initiation (patients 3,4,5, and 8) and all had been diabetic for at least one year prior to pump initiation with uncontrolled blood sugar, as is typical of this phase of life in diabetes..[15] There was a marked improvement in HbA1c in all patients. Specifically for this age group, it has been shown that the benefit of pump use will appear only 6-12 months of being on the pump.[18,19] Effectively, the benefit was seen in one patient who had been on the pump for 9 months. The small number of patients involved in our study does not allow us to generalize the effect of CSII on adolescents. Nevertheless, our results are supported by Bin-Abbas et al[20] who have shown the effectiveness of pump therapy in a group of 14

children and adolescents in Saudi Arabia, when they were shifted from MDI to CSII.

One of our type 1 diabetic patients was 3 months pregnant upon starting CSII, with no pregnancy related complications but there is no evidence that CSII offers any advantages in maternal or fetal outcomes when compared to conventional intensive insulin therapy using MDI[21] in patients with type1 diabetes during their pregnancy. CSII is safe and useful in controlling hyperglycemia in pregnant women with type 2 or gestational diabetes.[22] Pre-conception glycemic control seems to be the only factor affecting fetal malformations.
Thus, pump therapy seems effective across all subgroups, and with varying disease duration. In support of our findings, clinical studies favouring the use of CSII have been published for all age groups: preschoolers and toddlers,[14,15,23,24] children,[11-13] adolescents, [3,5,9,10] adults, and for pregnant patients[25] although the extent of evidence is not always homogenous among each group.

In our study, as in many observational ones, weight gain did not differ, but total insulin dose per kg body weight decreased significantly by 10%. Generally, the absolute daily insulin requirement increases significantly with age. It is 0.71 ± 1.31 unit/kg in the preschool period, 0.73±0.16 prepubertally, and 0.83 ± 0.19 unit/kg at adolescence.[26] Overall, there is a 14% reduction in daily insulin dose as compared to pre-pump use across all age groups except in toddlers.[27] The fact that the decrease in insulin dose post-pump in our population was more modest may be due to the fact that our population was uncontrolled at baseline, and may have been slightly underdosed on MDI (mean inuslin dose was 0.68 ± 0.23 units/kg/day). The total dose increase was limited by hypoglycemia on MDI. Thus, not only does the pump provide better glucose control/lower HbA1c, but also less weight gain/insulin requirement and less hypoglycemia.

What makes CSII so advantageous? The benefits of CSII are explained by at least two findings: firstly, less variability in peripheral absorption due to continuous infusion at the same site and due to the fact that monomeric short-acting insulin analogues, aspart or lispro are more stable in comparison to NPH or regular insulin.[3] Secondly, the rate of the infusion can be adjusted by 0.1 units/h allowing more flexibility and fine-tuning thereby conferring to continuous infusion many advantages such as a decreased risk of nocturnal hypoglycemia, better control of the dawn phenomenon, greater freedom in timing of meals and snacks, and decreased risk of activity-induced hypoglycemia.[4,5,7] Ultimately, lower HbA1c are expected as shown in a head-to-head comparison of MDI and CSII both using lispro as the short-acting insulin.[28]

This method of insulin delivery seems to be restricted to the privileged who can afford it. In one Lebanese center caring for around one thousand patients with type 1 diabetes, there are currently 30 pumps in use (0.3%). This is much less than the 20% of adult patients with type 1 diabetes mellitus using the pump in the United States.[29] The choice of health care professionals and patients to use CSII is limited by financial constraints: eighty-percent of the Lebanese population does not have third party coverage, and currently CSII cost is not covered by the National Ministry of Health. Thus, the financial burden lies mainly upon the patients and their families for the cost of supplies and medications.

Our study has many limitations: firstly, the small number of subjects studied does not allow us to draw conclusions about the general efficacy of CSII in our country. Secondly, patients who transferred to CSII were highly motivated and had the material means to do so. The results are likely to be affected by a 'selection' bias, which again would limit general applicability of pump use. Thirdly, three patients were lost to follow-up after feeling comfortable with their "pumps" and serial HbA1c concentrations over long periods could not be traced. Further longitudinal studies with a longer follow–up period (beyond 2 years) are required to assess the long-term efficacy of pump therapy in our country.

In summary, in the population studied, CSII was a well accepted method of insulin delivery. Our case series also demonstrates an improvement in glycemic control in patients with Type1 Diabetes who were transferred to it.

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; 329:977-986.
2. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000; 342: 381-389.
3. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005; 353:2643-2653.
4. Pickup JC, Keen H, Parsons JA, Alberti KG. Continuous subcutaneous insulin infusion: an approach to achieving normoglycaemia. Br Med J 1978;1: 204-207.
5. Tamborlane WV, Sherwin RS, Genel M, Felig P. Reduction to normal of plasma glucose in juvenile diabetes by subcutaneous administration of insulin with a portable infusion pump. N Engl J Med 1979; 300: 573-578.
6. Pickup J, Keen H. Continuous subcutaneous insulin infusion at 25 years: evidence base for the expanding use of insulin pump therapy in type 1 diabetes. Diabetes Care 2002; 25: 593-598.
7. Pickup J, Mattock M, Kerry S. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials. BMJ 2002; 324: 705.
8. Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R. Insulin pump therapy: a meta-

analysis. Diabetes Care 2003;26:1079-1087.
9. Hanaire-Broutin H, Melki V, Bessieres-Lacombe S, Tauber JP. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens using insulin lispro in type 1 diabetic patients on intensified treatment: a randomized study. The Study Group for the Development of Pump Therapy in Diabetes. Diabetes Care 2000; 23: 1232-1235.
10. Wainstein J, Metzger M, Wexler ID, et al. The use of continuous insulin delivery systems in severely insulin-resistant patients. Diabetes Care 2001; 24: 1299.
11. Wainstein J, Metzger M, Boaz M, et al. Insulin pump therapy vs. multiple daily injections in obese Type 2 diabetic patients. Diabet Med 2005; 22: 1037-1046.
12. Herman WH, Ilag LL, Johnson SL, et al. A clinical trial of continuous subcutaneous insulin infusion versus multiple daily injections in older adults with type 2 diabetes. Diabetes Care 2005; 28:1568-1573.
13. Ahern JA, Boland EA, Doane R, et al. Insulin pump therapy in pediatrics: a therapeutic alternative to safely lower HbA1c levels across all age groups. Pediatr Diabetes 2002; 3: 10-15.
14. Maniatis AK, Klingensmith GJ, Slover RH, et al. Continuous subcutaneous insulin infusion therapy for children and adolescents: an option for routine diabetes care. Pediatrics 2001; 107: 351-356.
15. Plotnick LP, Clark LM, Brancati FL, Erlinger T. Safety and effectiveness of insulin pump therapy in children and adolescents with type 1 diabetes. Diabetes Care 2003; 26: 1142-1146.
16. Implementation of treatment protocols in the Diabetes Control and Complications Trial. Diabetes Care 1995; 18: 361-376.
17. Springer D, Dziura J, Tamborlane WV, et al. Optimal control of type 1 diabetes mellitus in youth receiving intensive treatment. J Pediatr 2006; 149: 227-232.
18. Rewers A, Chase HP, Mackenzie T, et al. Predictors of acute complications in children with type 1 diabetes. Jama 2002; 287: 2511-2518.
19. Bulsara MK, Holman CD, Davis EA, Jones TW. The impact of a decade of changing treatment on rates of severe hypoglycemia in a population-based cohort of children with type 1 diabetes. Diabetes Care 2004; 27: 2293-2298.
20. Bin-Abbas BS, Sakati NA, Raef H, Al-Ashwal AA. Continuous subcutaneous insulin infusion in type 1 diabetic Saudi children. A comparison with conventional insulin therapy. Saudi Med J 2005; 26: 918-922.
21. Hieronimus S, Cupelli C, Bongain A, et al. [Pregnancy in type 1 diabetes: insulin pump versus intensified conventional therapy]. Gynecol Obstet Fertil 2005; 33: 389-394.
22. Simmons D, Thompson CF, Conroy C, Scott DJ. Use of insulin pumps in pregnancies complicated by type 2 diabetes and gestational diabetes in a multiethnic community. Diabetes Care 2001; 24: 2078-2082.
23. Weintrob N, Benzaquen H, Galatzer A, et al. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens in children with type 1 diabetes: a randomized open crossover trial. Pediatrics 2003; 112 :559-564.
24. Wilson DM, Buckingham BA, Kunselman EL, et al. A two-center randomized controlled feasibility trial of insulin pump therapy in young children with diabetes. Diabetes Care 2005; 28: 15-19.
25. Doyle EA, Weinzimer SA, Steffen AT, et al. A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. Diabetes Care 2004; 27: 1554-1558.
26. Danne T, Battelino T, Kordonouri O, et al. A cross-sectional international survey of continuous subcutaneous insulin infusion in 377 children and adolescents with type 1 diabetes mellitus from 10 countries. Pediatr Diabetes 2005; 6: 193-198.
27. Litton J, Rice A, Friedman N, et al. Insulin pump therapy in toddlers and preschool children with type 1 diabetes mellitus. J Pediatr 2002; 141: 490-495.
28. Boland EA, Grey M, Oesterle A, et al. 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; 22:1779-1784.
29. Pickup JC: Long-term use of continuous subcutaneous insulin infusion. Diabetes Res Clin Pract 2006;74 Suppl 2:S101-103.