

Original Research Article

Comparison of effectiveness of continuous subcutaneous insulin infusion with daily insulin injection in a Chinese population of Type I diabetic patients

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Abstract

Purpose: To compare the clinical effectiveness of continuous subcutaneous insulin infusion therapy with that of multiple-dose insulin therapy in type 1 diabetic patients.

Methods: A total of 1000 type 1 diabetic patients were assigned to two groups, with 500 patients per group. Patients in group I were treated with continuous subcutaneous infusion of insulin (CSII), while those in group II received multiple daily doses of insulin injection. Body mass index (BMI), insulin dose, HbA1c levels, and frequencies of hypoglycemia and diabetic-ketoacidosis (DKA) were determined in each patient at baseline, and at 4-week intervals for 4 years.

Results: The HbA1c levels at baseline and at the end of 4th year in group I were 8.9 ± 1.1 and 8.2 ± 1.5 %, respectively, relative to corresponding values of 8.6 ± 1.2 and 9.1 ± 1.1 %, respectively in group II. The results revealed significant difference in HbA1c between the two groups ($p < 0.05$). After 4 years of therapy, insulin requirement was markedly higher in group II than at baseline (0.8 ± 0.1 vs 0.9 ± 0.2 , $p < 0.05$) IU/kg/day. However, insulin requirement in group I decreased after 4 years, relative to that at baseline (0.65 ± 0.2 vs 0.8 ± 0.1 IU/kg/day; $p < 0.05$).

Conclusion: CSII therapy seems to be an effective and safe gold standard method for managing type I diabetes mellitus patients.

Keywords: Type I diabetes, Continuous subcutaneous insulin infusion therapy, HbA1c, Hypoglycemic events

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INTRODUCTION

Worldwide, type I diabetes mellitus (T1DM) is a chronic disease which affects nearly half a million children. Although advanced delivery of insulin and accessibility to various types of insulin have been developed, the levels of HbA1c still remain significantly high in majority of the affected children [1].

Glycemic control in Type I diabetic patients is considered to be a major and important factor for the growth and proper development of the child. Multiple daily doses of insulin are considered as the standard and popular approach in the treatment of type 1 diabetic patients. However, hypoglycemic events and obesity are regular adverse events associated with multiple-dose

insulin therapy [1]. Since the year 2000, continuous subcutaneous infusion of insulin (CSII) has been in use by many clinicians [2]. Many researchers have reported that CSII therapy reduced the risk of hypoglycemia and minimized DKA, leading to the suggestion that CSII therapy should be used in children and adolescents [2-4].

Some long-term studies also revealed that continuous subcutaneous infusion of insulin was correlated with lower incidence of diabetic complications and reduction in diabetes-related mortality, when compared with daily multiple doses of insulin [5,6].

China reported approximately 110 million diabetes mellitus patients in 2018, accounting for the highest number diabetes mellitus cases in the world [7]. Researchers have advised that clinicians should prescribe CSII therapy for type 1 diabetic patients who are able to assess blood glucose levels for a minimum of 4 times a day via self-monitoring, and those who can comply with dietary protocols, having successfully completed a course on carbohydrate (calorie) restriction.

Diabetes control and complication trials suggest that patients on CSII therapy should monitor their blood sugar level a minimum of 4 times a day [8,9]. In clinical practice, the appropriate number of injections can be provided easily, but comprehensive management involving intensive one-on-one supervision, diet control, psychological counseling, and insulin dose adjustment are difficult to achieve [8,9]. The aim of this study was to compare the effects of CSII and multiple daily-dose insulin therapy on type 1 diabetes mellitus patients, with respect to insulin requirement, blood sugar control and body mass index (BMI).

EXPERIMENTAL

The total sample size in this study comprised 1000 diabetic type 1 patients treated in our hospital. Ethical approval for the study was obtained from The First People's Hospital of Yichang Ethics and Research Board (approval no. FPH/2016/M-45). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines [10]. Informed consent was obtained from every participant before starting the trial. The patients were assigned to 2 groups, with 500 patients per group. Group I patients were treated with CSII, while group II patients were treated with multiple daily-dose insulin administration.

The inclusion criteria used in this study were: (1) Availability of pre-clinical data for the patient, (2) availability of pre-treatment biochemical data such as HbA1c level, height and weight of the patient; (3) complete record of patient's follow up; (4) evidence of a minimum of six months of CSII therapy before enrollment in the study, and (6) evidence that the patient did not use multiple daily-dose insulin therapy and CSII.

Standard protocol was followed in the diagnosis of Type I diabetic mellitus in patients. The diagnosis was based on the guidelines of International Diabetic Federation ISPAD/IDF. The protocol used in this therapy involved daily insulin therapy, with 3-4 injections of short- and long-acting insulin analogs per day. The measurement of blood sugar level was done 3-4 times at home using self-measurement method.

In CSII therapy, Medtronic MiniMed pump (Carelink Minmed, California, USA) was used. All patients in CSII group, except one, used the ultrashort-acting type of insulin therapy.

Patients in both groups were assessed every 4th week. The study was conducted for long-term assessment, and all the patients were followed up for 4 years. Body mass index (BMI), insulin dose, HbA1c level, hypoglycemic events, and diabetic-ketoacidosis in each patient were determined and recorded at baseline and after every 4 weeks for 4 years of follow up. Adverse events such as allergic reactions, bruising and bleeding were also recorded in the two groups. On each visit, height, weight, BMI, insulin level and HbA1c level were determined. Tosoh analyzer marker was used to assess the HbA1c levels, with normal range kept at 4.2-6.1%, mean level at 5.6%, and inter-assay SD of 0.013 %. Patients showing serum pH more than 7.2, with ketonemia and bi-carbonate higher than 16 mmol/L, were considered to have positive signs of diabetic ketoacidosis.

A training workshop was organized for every patient for CSII therapy, as well as their caregivers. The workshop covered the principles of operation of the insulin pump, insertion technique, blousing of the insulin and carb counting. Training on carb counting was provided to all patients by experienced dieticians. Patients were advised to check their blood sugar level before and after meals, at 12:00 midnight and at 3:00 am. Initial dose for the CSII therapy was adjusted to 80 % of the daily dose of insulin for multiple-dose insulin therapy procedure. The dose of insulin was adjusted according to the daily activity of the patients and pattern of blood sugar level.

The infusion set was replaced every 3 days. Occlusion of the catheter which could be associated with high blood glucose level, was also monitored in this study. In this case, the patients were advised to take the insulin via the conventional injection technique, and the infusion set was replaced.

Statistical analysis

The SPSS software (version 20.0) was used for statistical analysis. Data values are expressed as mean ± SD. Mann Whitney U test was used to compare HbA1c levels between the baseline and follow-up in both groups. Student t-test was used to compare the mean values of normally distributed variables between the groups. Values of p < 0.05 were taken as indicative of statistical significance.

RESULTS

The baseline characteristics of patients in the two groups are shown in Table 1. There were no significant differences in baseline characteristics such as mean age, distribution of gender, insulin dose, HbA1c, BMI and duration of type 1 diabetes between the two groups.

The patients reported that CSII therapy provided significantly better care and improved quality of life via effective blood sugar control, when compared to MDI therapy. Moreover, there were markedly lower incidence of adverse events and less ketoacidosis in group I patients than in group II patients (p < 0.05).

The results of the study also revealed that the HbA1c levels declined in the first year in both groups after the start of treatment. However, after the end of the 2nd year, group II patients showed increased levels of HbA1c, which exceeded the baseline level after 4 years of therapy (8.6±1.2 mmol/L at baseline vs. 9.1 ± 1.1 mmol/L in 4th year; p < 0.05). These results are shown Figure 1.

The HbA1c levels at baseline and at the end of 4 years in group I were 8.9±1.1 and 8.2±1.5, respectively, while the corresponding values for group II were 8.6±1.2 and 9.1±1.1, respectively (p < 0.05).

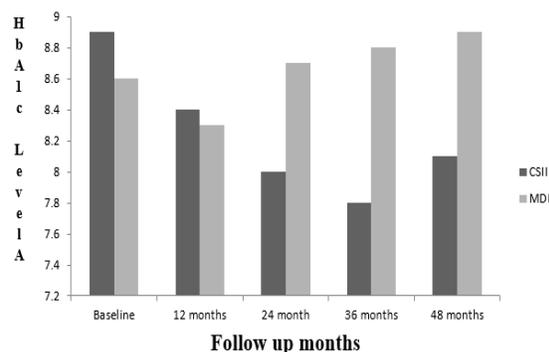


Figure 1: Changes in levels of HbA1c in both groups over 4 years of therapy

This study revealed no significant differences in levels of HbA1c between male and female patients in each group, at baseline and during the follow up period of 4 years. The mean dose of insulin at baseline in group I (0.8 ± 0.1) was comparable to that of group II (0.8 ± 0.1).

Table 1: Basic characteristics of patients in the studies groups

Characteristic	CSII (n=500)	MDI (n=500)	P-value
Gender*			
Male	188 (37.6)	172 (34.4)	0.167
Female	312 (62.4)	328 (65.6)	0.543
Age at entry (years)	9.1±1.4	9.8±1.5	0.111
BMI (kg/m ²)	17.4±4.1	17.8±4.7	0.767
Duration of diabetes at entry (years)	5.8±1.3	5.9±1.3	0.187
Insulin dose (U/kg/day)	0.8±0.1	0.8±0.1	0.777
HbA1c (%)	8.9±1.1	8.6±1.2	0.651
Outcomes in Groups I and II			
Better control	275 (55)	145 (29)	<0.05
Frequent hypoglycemia	50 (10.0)	180 (36)	<0.05
Dislike/fear of needles	40 (8.0)	105 (21)	>0.05
Better quality of life	105 (21)	45 (9)	<0.05
Recurrent DKA	15 (3.0)	25 (5)	>0.05
Others	15 (3.0)	0 (0)	>0.05

Moreover, after first six months, insulin requirement in each group was reduced to the same level (0.7 ± 0.2). After 4 years of therapy, insulin requirement in group II was significantly higher than the baseline level (0.8 ± 0.1 vs 0.9 ± 0.2 ; ($p < 0.05$). In contrast, after 4 years, insulin requirement in group I was decreased, when compared to baseline value (0.65 ± 0.2 vs 0.8 ± 0.1 ; ($p < 0.05$). These results are presented in Table 2.

Table 2: Changes in daily insulin requirement in CSII and MDI groups

Time span (months)	Group I	Group II
Baseline	0.8 ± 0.1 IU/Kg/Day	0.8 ± 0.1
12	0.7 ± 0.2 IU/Kg/Day	0.7 ± 0.2
24	0.71 ± 0.2 IU/Kg/Day	0.78 ± 0.2
36	0.7 ± 0.2 IU/Kg/Day	0.81 ± 0.2
48	0.65 ± 0.2 IU/Kg/Day	0.9 ± 0.2

As shown in Table 3, basal metabolic rate was similar in both groups at baseline, but it was increased after the first year of therapy in both groups. However, the increase in basal metabolic rate in group I after 4 years was higher than that in group II (0.9 vs 1.6 ; $p < 0.05$). There was no significant difference in BMI between male and female patients. Moreover, there were no significant changes in triglyceride levels and blood pressure in both the groups at the baseline and after 4 years.

Table 3: Changes in BMI in CSII and MDI groups

Time span (month)	Group I	Group II
Baseline	0.6 ± 0.1 kg/m ²	0.6 ± 0.1
12	0.8 ± 0.2 kg/m ²	0.7 ± 0.2
24	0.85 ± 0.2 kg/m ²	0.71 ± 0.2
36	0.89 ± 0.2 kg/m ²	0.77 ± 0.2
48	0.9 ± 0.2 kg/m ²	0.76 ± 0.2

The number of hypoglycemic events reported at baseline in group I patients was 9.5 in 100 patients. However, after 4 years of CSII therapy, the number of hypoglycemic events was decreased to 3.4 events in 100 patients, relative to 8.4 events per 100 patients in group II at baseline ($p < 0.05$). However, after 4 years of daily dose of insulin, the number of hypoglycemic events increased to 20.1 ($p < 0.05$).

The incidence of diabetic ketoacidosis was also decreased in group I after 4 years of CSII, but the decrease was not significant (5.1 vs 2.1 events/100 patients). In addition, the incidence of diabetic ketoacidosis was not decreased in group II.

There was lower incidence of complications such as skin erythema on the site of cannula insertion and bruising in the CSII therapy, than in MDI group. However only one patient developed infection from local antibiotics. These events were reported within the first 2 years of treatment, but they resolved after 3 months.

DISCUSSION

This is the first ever long-term study conducted on a large Chinese population to compare the efficacy of CSII therapy with that of daily-dose insulin therapy in the management of blood sugar.

The results clearly showed continuous and significant improvements in blood sugar level (with HbA1c as index) in Group I, when compared to group II. Previous studies have also demonstrated that CSII therapy is far better than multiple daily-dose insulin therapy [11,12]. The risk of hypoglycemic events was also lower in group I than in group II. This is consistent with a previous report which showed that CSII therapy in age- and gender-matched group of patients provided a better blood glucose control than insulin injections [13].

In this study, there was no significant difference in HbA1c level between and female patients throughout the study period. This finding is consistent with that of an earlier study [14]. However, in another study, it was reported that males showed a better glycemic control with CSII therapy than females [15]. The researchers revealed that it was very difficult to control blood sugar level in females because they were at high risk of depression.

In this study, it was shown that type I DM children under the age of 6 showed better glycemic control than those aged more than 6. This finding is in agreement with some other reports [16,17]. The possible reason could be that children of this age are usually totally under the supervision of care givers who are responsible for giving the treatments at the proper time, checking blood sugar level, carb counting, and careful entry of pump data. In contrast, children of higher ages rely less on caregivers. However, a study has revealed no correlation between age and HbA1c levels [13].

This study showed that children treated with CSII required lower doses of insulin throughout the period of the study than children on daily-dose insulin therapy. A similar result was obtained in previous investigations [14,18] This could be explained by the fact that CSII therapy closely

monitors physiological secretion of insulin. Thus, less level of insulin is required to control blood sugar level, when compared to daily-dose insulin therapy.

Some researchers have revealed that CSII therapy produced weight increase in patients [19-21]. In contrast, the present study revealed significant increase in BMR, and significant reduction in body weight after 4 years of therapy. The CSII therapy improved glycemic control, but this was not associated with hypoglycemic events. Moreover, there was significant reduction in severe hypoglycemic events in CSII therapy, relative to daily dose of insulin throughout the study period. This observation is inconsistent with the observations in many studies [7,11,22]. The reason behind this variation is that insulin pump is more physiological, and it adjusts the BMR more closely while patients are sleeping and doing some activity. There was no difference in cases of diabetic ketoacidosis (DKA) between the two groups after the 4 years of the therapy, although DKA was less in group I than in group II. In contrast, in another study, it was reported that DKA events were increased from 0.07 to 0.1 per 100 patients [14]. The long-term follow-up period and large sample size used in this study make it different from other previous studies, and revealed a strong clinical implication of the findings.

Limitations of the study

The lack of randomization between group I and group II could be considered a limitation in this study. This study assessed the patients every 4 weeks for 4 years with proper protocol. However, the total number of visits by each patient was not monitored. This could affect the glycemic control. Extra education on CSII use could have reduced the prevalence of adverse events and improved glycemic control, although this should be set in the context of adult study

INPUT, which reported no effect of a structure education programme on glycaemic control in patients treated with CSII.

CONCLUSION

This study has shown that CSII therapy is an effective and safe gold standard method for managing type I diabetes mellitus patients. The therapy allows for continuous monitoring of blood sugar levels. The best feature of the therapy is that it also reduces the frequency of hypoglycemic events. There is need for significant active participation of patients and

their caregivers to maximize the beneficial effects of this therapy.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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REFERENCES

1. Kordonouri O, Hartmann R, Danne T. Treatment of type 1 diabetes in children and adolescents using modern insulin pumps. *Diabetes Res Clin Pract* 2011; 93(Suppl 1): S118-S124 70027-70034.
2. Skinner TC, Cameron FJ. Improving glycaemic control in children and adolescents: which aspects of therapy really matter. *Diabet Med* 2010; 27(4): 369-375.
3. Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R. Insulin pump therapy: a meta-analysis. *Diabetes Care* 2003; 26(4): 1079-1087.
4. DiMeglio LA, Pottorff TM, Boyd SR, France L, Fineberg N, Eugster EA. A randomized, controlled study of insulin pump therapy in diabetic preschoolers. *J Pediatr* 2004; 145(3): 380-384.
5. 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(7339): 705.

6. 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; 22(11): 1779-1784.
7. Hanas R, Lindgren F, Lindblad B. A 2-yr national population study of pediatric ketoacidosis in Sweden: predisposing conditions and insulin pump use. *Pediatr Diabetes* 2009; 10(1): 33-37.
8. Ronald C, W Ma. Epidemiology of diabetes and diabetic complications in China. *Diabetologia* 2018; 61: 1249–1260.
9. Majedah M, AbdulRasoul Mohammad M, Maria Al-M, Hala Al-Sanaa, Dalia Al-AbdulRazzaq, and Hessa Al-Kandari. A Comparison of Continuous Subcutaneous Insulin Infusion vs. Multiple Daily Insulin Injection in Children with Type I Diabetes in Kuwait: Glycemic Control, Insulin Requirement, and BMI. *Oman Med J* 2015 Sep; 30(5): 336–343.
10. General Assembly of the World Medical Association: World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects *J Am Coll Dent Summer* 2014;81(3):14-8.
11. 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(4): 1142-1146.
12. Hanas R, Lindgren F, Lindblad B. A 2-yr national population study of pediatric ketoacidosis in Sweden: predisposing conditions and insulin pump use. *Pediatr Diabetes* 2009; 10(1) :33-37.
13. Johnson SR, Cooper MN, Jones TW, Davis EA. Long-term outcome of insulin pump therapy in children with type 1 diabetes assessed in a large population-based case-control study. *Diabetologia* 2013; 56(11): 2392-2400.
14. Shalitin S, Gil M, Nimri R, de Vries L, Gavan MY, Phillip M. Predictors of glycaemic control in patients with Type 1 diabetes commencing continuous subcutaneous insulin infusion therapy. *Diabet Med* 2010; 27(3): 339-347.
15. Mameli C, Scaramuzza AE, Ho J, Cardona-Hernandez R, Suarez-Ortega L, Zuccotti GV. A 7-year follow-up retrospective, international, multicenter study of insulin pump therapy in children and adolescents with type 1 diabetes. *Acta Diabetol* 2014. Apr;51(2):205-210.
16. Doyle EA, Weinzimer SA, Steffen AT, Ahern JA, Vincent M, Tamborlane WV. A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. *Diabetes Care* 2004; 27(7): 1554-1558.
17. Ahern JA, Boland EA, Doane R, Ahern JJ, Rose P, Vincent M, Tamborlane W. Insulin pump therapy in pediatrics: a therapeutic alternative to safely lower HbA1c levels across all age groups. *Pediatr Diabetes* 2002; 3(1) :10-15
18. Jeitler K, Horvath K, Berghold A, Gratzner TW, Neeser K, Pieber TR, A Siebenhofer. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. *Diabetologia* 2008; 51(6): 941-951.
19. Hathout EH, McClintock T, Sharkey J, Kytzenko D, Hartwick N, Hadley-Scofield M, Torgeson S, Mace JW. Glycemic, auxologic, and seasonal aspects of continuous subcutaneous insulin infusion therapy in children and young adults with type 1 diabetes. *Diabetes Technol Ther* 2003; 5(2): 175-181
20. Battelino T. Risk and benefits of continuous subcutaneous insulin infusion (CSII) treatment in school children and adolescents. *Pediatr Diabetes* 2006; 7(Suppl 4): 20-2.
21. Sulli N, Shashaj B. Long-term benefits of continuous subcutaneous insulin infusion in children with Type 1 diabetes: a 4-year follow-up. *Diabet Med* 2006. Aug;23(8):900-906.
22. Deiss D, Hartmann R, Hoeffe J, Kordonouri O. Assessment of glycemic control by continuous glucose monitoring system in 50 children with type 1 diabetes starting on insulin pump therapy. *Pediatr Diabetes* 2004. Sep; 5(3): 117-121.