Diabetologia (1989) 32: 421-426

Diabetologia

Long-term safety, efficacy and side-effects of continuous subcutaneous insulin infusion treatment for Type 1 (insulin-dependent) diabetes mellitus: a one centre experience

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Summary. A follow-up study of 116 Type 1 (insulin-dependent) diabetic patients on long-term continuous subcutaneous insulin infusion was conducted after 4.5 ± 0.2 years. The average HbA_{1c}-value of these patients decreased by 1% to $6.7 \pm 0.1\%$ during this observation period. Typical side effects of continuous subcutaneous insulin infusion such as skin inflammation at the catheter insertion site occurred with similar frequency as has been reported previously by other authors. Diabetic ketoacidosis (0.14 per patient year) and disabling hypoglycaemia (0.1 per patient year, including 0.05 hypoglycaemic coma per patient-year) occurred at substantially lower rates than in other comparable studies with Type 1 diabetic patients at a similar degree of metabolic control. Subgroup evaluation suggested that a normal ($< 5.6\%$) HbA_{1c}-value at follow-up was associated with increased incidence of disabling hypoglycaemia, whereas poor metabolic control ($HbA_{1c} > 7.5\%$) was associated with increased rates of skin complications and hospital treatment for ketoacidosis. Thus, under the policies of this diabetes centre, continuous subcutaneous insulin infusion has proved to be beneficial to a large proportion of experienced adult Type 1 diabetic patients, who voluntarily had opted for, and continued with, this particular mode of insulin treatment.

Key words: Insulin therapy, insulin pumps, diabetes complications, blood glucose self-monitoring, diabetes diet.

Four years after Slama et al. had introduced continuous ambulatory i.v. infusion of regular insulin into diabetes management [1], Pickup et al. in 1978 modified this approach into continuous subcutaneous insulin infusion (CSII) therapy with portable mini-pumps [2]. This method was approved in 1985 by the American Diabetes Association [3] as an alternative to conventional insulin injection therapy for the treatment of Type 1 (insulin-dependent) diabetes mellitus.

Improvement in acute metabolic control which may be achieved with CSII compared to conventional insulin therapy [4-7], as well as side effects of CSII (diabetic ketoacidosis, severe hypoglycaemia and skin complications at the catheter insertion site [4]) have been noted. Little is known as to the long-term efficacy of CSII therapy, most of the previous papers providing intermediate-term observations at best [4-13]. Only a few studies have reported follow-up results of more than two years [14-18], some of these with rather disappointing results, e.g. frequent failure to maintain improved metabolic control, a high rate of rejection of CSII by the patients [14, 17] and a number of deaths have been associated with long-term CSII [15, 17, 18]. These drawbacks could either have been caused by the technique of CSII itself, or by the particular conditions of care offered by the different diabetes centres conducting CSII. The aim of the present study was, therefore, to investigate the feasibility and outcome of CSII over an extended period of time, with particular respect to the treatment conditions as offered by our diabetes centre.

Subjects and methods

All 140 patients with Type 1 diabetes [19] who had been initiated on CSII according to the Helsinki Declaration [20] at our department between March 1980 and May 1986 were followed-up between June and December 1987. At follow-up, 24 of the 140 patients had resumed insulin injection therapy; their clinical data, with the obvious exception of them still being alive and having discontinued CSII therapy, was incomplete and will therefore not be considered in this report.

We re-examined all 116 patients continuing CSII at the time of follow-up after 1-7 years, i.e. after a mean of 4.5 ± 0.2 years, giving a total observation time of 518 patient-years of CSII. The social status of the patients, 60 men and 56 women, was as follows: 62 employees, 18 housewives, 17 students, 10 self-employed, 8 retirees and 1 unemployed patient. The age of the patients at the beginning of CSII was 29 ± 1 years and the duration of diabetes was 14 ± 1 years. Twenty-two patients (19%) had random C-peptide levels ≥ 0.4 ng/ml, 48 patients (41%) had clinical evidence of diabetic late complications. Ten patients received antihypertensive treatment. For further details see Table 1.

Table 1. Clinical characteristics of the 116 patients studied before and after a mean of 4.5 years of continuous subcutaneous insulin infusion treatment (means ± SEM)

	Initial fasting values	Follow-up non-fasting values
Weight (kg)	68.3 ± 0.7	70.6 ± 0.8[a]
Body mass index (kg/m^2)	22.9 ± 0.2	23.6 ± 0.2[a]
Total cholesterol (mmol/l)	5.13 ± 0.1	5.35 ± 0.1
HDL-cholesterol (mmol/l)	1.33 ± 0.03	1.43 ± 0.05
Triglycerides (mmol/l)	1.13 ± 0.05	1.46 ± 0.13[a]
Serum-creatinine (μmol/l)	89 ± 2	84 ± 3
HbA_{1c} (%)	7.7 ± 0.1	6.7 0.1[a]
Blood pressure (mm Hg)		
systolic	125 ± 1	128 ± 1[a]
diastolic	80 ± 1	81 ± 1

[a] denotes significant difference between means at $p < 0.05$

Therapeutic principles and definitions

Principles of CSII technology [4, 21–26], and particular aspects of CSII therapy as offered by this department [11, 25–27] have been published previously. We initiated CSII only at the request of patients already familiar with intensified insulin injection therapy [28, 29]. These patients wanted to try CSII for further improvement of HbA_{1c} levels, or for more flexibility of life-style, which they had been unable to achieve with multiple injection therapy.

For the purpose of this study, diabetic ketoacidosis (DKA) was defined as nausea or vomiting in the presence of hyperglycaemia (blood glucose above 13 mmol/l) and moderate or severe ketonuria. In this case, patients were instructed that extra insulin should be given subcutaneously by insulin syringe (e.g. 10 U of regular insulin every hour until the symptoms disappeared).

Disabling hypoglycaemia (DH) was defined as a state of neuroglycopenia leading to an impairment or loss of consciousness with the need for external help. DH was to be prevented, e.g. by an appropriate reduction of insulin dosage in relation to heavy exercise, and a target level of fasting blood glucose ≥ 5.0 mmol/l, since lower fasting glycaemia during CSII may be associated with substantial hyperinsulinaemia [25, 30] and nocturnal hypoglycaemia. To prevent late postprandial hypoglycaemia due to inappropriately high doses of prandial insulin, the portion of carbohydrates per meal should not exceed 80–100 g and the required insulin bolus therefore should not exceed 10–15 U. Blood glucose self-monitoring (BGSM) should be performed before each main meal, and if possible, before each single insulin bolus and at bed-time. Diet could be liberalised to a certain extent [11, 31, 32] as described previously. Recommendations as to the handling of the insulin infusion catheters have been changed slightly over the years. Since 1986, polyethylene-made rather than PVC-made catheters [33], with skin disinfection before catheter insertion [27] have been advised. The catheters should be renewed every 2 to 3 days, and should not be reused. Only insulin pumps with satisfactory precision allowing changes in basal infusion rates (approximately 1 U/day), with alarm functions, and with acceptable feasibility of handling have been recommended at this centre [34]. Pumps from 8 different manufacturers were used. Human and porcine regular insulins from four different manufacturers (Novo, Bagsvaerd, Denmark; Nordisk, Gentofte, Denmark; Eli Lilly Corp., Giessen, FRG; Hoechst, Frankfurt, FRG) in concentrations of 40 U/ml and 100 U/ml were used. All costs for CSII treatment (i.e. for the devices, the initial hospital stay, cannulas, dressings insulin, BGSM test strips, skin disinfectant) were covered by the patients' health insurance. The patients were offered routine diabetes care at our diabetes outpatient clinic every weekday morning, and Monday and Thursday evenings. A 24-h telephone service providing contact with a diabetes nurse or physician was also available.

Methods

Baseline data (obtained under fasting conditions) were taken from the clinical records of the 116 patients at initiation of CSII. The follow-up investigations were carried out in our outpatient clinic ($n = 96$) or in the patients' homes ($n = 20$). A standardised questionnaire was completed concerning details of their dietary habits, and of their current and previous CSII therapy, particularly the occurrence, causes, and management of DKA and DH. Hospitalisation for diabetes-related and un-related causes was also evaluated by the questionnaire, if necessary additional information was obtained from the patients records kept either by our outpatient clinic ($n = 82$), by their family physicians ($n = 29$), or by other hospitals ($n = 5$). The patients were asked to present their diabetes diaries for analysis of their entries [28, 29]. Under random, non-fasting conditions, bodily measurements were taken, and a venous blood sample was drawn for determination of HLA-status, plasma glucose, blood lipids, creatinine and C-peptide, using routine laboratory methods, and for determination of HbA_{1c}. The insulin infusion sites were also inspected.

HbA_{1c} was determined previously in our laboratory by the modified thiobarbiturate (TBA) method [28, 36]. In 1986, this method was replaced by HPLC-determination [35, 36], using the Diamat Analyser (Biorad Laboratories, Munich, FRG) [37] with a normal mean HbA_{1c} of 4.83 (standard deviation 0.31)% of total Hb. In order to compare the TBA determined values with HPLC determined values, the former were converted into the latter by the formula given by Mecklenburg et al. [15]. A spot urine sample was obtained for measurement of proteinuria using a laser-turbidimetric method [38].

Statistical analysis

Means ± SEM are given, unless otherwise stated. Comparisons were performed with Chi-square, and t-test when appropriate. A p-value of < 0.05 was considered statistically significant. For subgroup analysis, standardised incidence ratios and 95% confidence intervals were calculated according to Morris and Gardner [39] by the use of Poisson distribution tables.

Results

Clinical characteristics (Table 1)

After 4.5 ± 0.2 years of CSII, all 116 patients were still alive. Their HbA_{1c} had decreased significantly from 7.7 ± 0.1% to 6.7 ± 0.1% at follow-up ($p < 0.001$). On the other hand, body mass index, and blood lipids were slightly elevated compared to the initial data, due to the fact that random (post prandial) measurements were taken at follow-up with the patients in street clothing, but fasting measurements were taken with the patients in underwear at initiation of CSII.

The patients random plasma glucose at follow-up was 6.4 ± 0.4 mmol/l; other blood chemistry showed that 5 patients had serum creatinine ≥ 110 μmol/l. Urinalysis showed 86 patients with normal proteinuria (< 50 mg/l), and 6 patients with macro-proteinuria (> 500 mg/l) at follow-up.

Diet parameters and insulin dosage

The patients reported having 3.9 ± 0.1 daily meals, with an average carbohydrate intake of 160 ± 5 g/day. Fifty percent of patients reported never drinking alcohol, whereas 7% of patients drank alcohol every day. The current basal insulin infusion rate at follow-up was 21.8 ± 0.6 U per day, and the total daily insulin dosage 41.8 ± 1.0 U, i.e. approximately 0.6 U/kg body weight.

Diabetic ketoacidosis (DKA)

There were 74 episodes of DKA during the total follow-up period of 518 patient years of CSII, i.e. an annual incidence of 0.14 DKA per patient. Thirty-four cases of DKA (0.06 DKA per patient-year) were treated in hospital; the remaining 40 cases were treated at home by repeated s.c. injection of regular insulin by the patients themselves, or relatives and friends. The 24-h telephone service had been contacted in only 15 of the DKA cases. Catheter defects (e.g. disconnected tubing) or inflamed insulin infusion sites were the main reasons for DKA (40% of cases). In 20% of cases, febrile illness was reported as the precipitating cause, whilst in the remaining 30 cases, no obvious cause was reported by the patients.

Disabling hypoglycaemia (DH)

There were 54 cases of DH during the 518 patient years, i.e. an annual incidence of 0.10 per patient. Hospital treatment or calling for an emergency care physician to inject glucose i.v. was necessary in 19 cases of DH (0.04 per patient-year), whereas the remaining 35 cases were managed by relatives or friends injecting glucagon ($n=8$) or giving oral carbohydrate. Hypoglycaemic coma occurred 0.05 times per patient-year. All cases of DH recovered without further problems. The predominating reasons for DH were accidental overdoses of prandial insulin ($n=20$) and exercise ($n=12$). During pregnancies, 4 DH occurred, and 8 DH were reported in relation to alcohol ingestion. Unidentified causes of DH ($n=10$) may include cases of circulating anti-insulin antibodies [24] or malfunction and mismanagement of the devices.

Skin complications

The patients reported a total of 134 cases of s.c. inflammation, i.e. 0.26 cases of inflammation per patient-year, 35 of which required antibiotic treatment and/or surgery. At follow-up examination, 48% of the patients had whitish scars on their abdominal skin, described as being the result of previous infections of the insulin infusion sites [27]. On inspection, in 51% of the patients erythema was present at the insertion site of the catheter needle currently used, subcutaneous nodules were palpable in 19%, and inflammation requiring antibiotic treatment was found in 1.7% of the patients.

Hospitalisation

During the 518 patient-years of follow-up, 77 out of 116 patients (66%) were hospitalised for diabetes-related and un-related causes for a total of 1606 days. Of these 3.1 days per patient-year in hospital a total of 1.0 days were related to 18 pregnancies, with the remaining 2.1 days being due to the treatment of metabolic disturbance, various operations, injuries, and treatment of diabetic eye disease.

Subgroup description

In order to identify possible associations between the degree of metabolic control and patients' characteristics and complications of CSII, patients were grouped deliberately according to their HbA_{1c} at follow-up: 16 patients (14%) with normal HbA_{1c} *(normal metabolic control)* represented 70 patient-years. Twenty-eight patients (24%) with HbA_{1c} between 5.6% and 6.25% *(excellent control)* represented 115 patient-years; 53 patients (46%) with HbA_{1c} between 6.26 and 7.5 *(good control)* represented 246 patient-years. The remaining 19 patients (16%) with HbA_{1c} exceeding 7.5% *(poor control)* represented 87 patient-years.

There were no differences between these four groups with respect to sex, age, HLA-status (data not shown), duration of diabetes, duration of CSII, prevalence of late diabetic complications, or the prevalence of serum-C-peptide $\geqslant 0.4$ ng/ml. Also, present non-smokers and non-drinkers (approximately 50% in each group) as well as patients drinking alcohol daily, were evenly distributed between the groups. For further details of patient characteristics, see Table 2. There were no differences between these patient groups with respect to insulin dosage, meal frequency (2 to 5 per day), renewal of catheters (2 to 4 times per week), and outpatient clinic visits (1 to 12 times per year). *Poorly controlled* patients, however, differed with regard to the incidence of treatment complications. *Poorly controlled* patients reported more cases of inflammation of the infusion site and were hospitalised more often for treatment of DKA than patients with normal HbA_{1c}, whereas patients with normal HbA_{1c} reported more cases of disabling hypoglycaemia (Table 3). Mean annual duration of hospitalisation for any reason was 4.0 days in patients with normal HbA_{1c}, 3.1 days in patients with excellent control, 3.0 days in patients with good control and 2.7 days in patients with poor control (NS).

Discussion

The present study confirms previous short-term observations [5–7, 9–13, 40] that CSII is effective in improving metabolic control in Type 1 diabetes. In our study, CSII was accepted and maintained as routine therapy for a mean of 4.5 years by 83% of patients in whom it

Table 2. Characteristics of continuous subcutaneous insulin infusion treatment as observed in patients with normal, excellent, good, and poor metabolic control at follow-up

	HbA_{1c}-value			
	< 5.6%	5.6-6.25%	6.26-7.5%	> 7.5%
Metabolic control	Normal	Excellent	Good	Poor
No. of patients	$n=16$	$n=28$	$n=53$	$n=19$
% of patients performing blood glucose self-monitoring approx.				
< 3/day	0%	4%	11%	11%
3-5/day	63%	86%	79%	79%
% of patients keeping a diabetes diary	75%	64%	76%	53%
% of patients using				
U-100 insulin[a]	75%	50%	57%	74%
U-40 insulin[a]	25%	50%	43%	26%
% of patients using stepped up supplementary infusion rate at dawn	13%	21%	8%	5%

[a] U-100/U-40 denotes the insulin concentration in units/ml

Table 3. Incidence of complications of continuous subcutaneous insulin infusion per patient-year, according to normal, excellent, good, and poor metabolic control at follow-up

	HbA_{1c}-value at follow-up			
	< 5.6%	5.6-6.25%	6.26-7.5%	> 7.5%
Metabolic control	Normal	Excellent	Good	Poor
Diabetic ketoacidosis (all)	0.142	0.113	0.146	0.172
Diabetic ketoacidosis (requiring in-hospital treatment)	0.014	0.052	0.073	0.104
Disabling hypoglycaemia	0.242[a]	0.147	0.065[b]	0.042[b]
Subcutaneous inflammation at the needle site	0.114[a]	0.156[a]	0.272	0.471[b]

[a] significantly different at $p<0.05$ as compared to [b] in the same line

was initiated. The mean HbA_{1c} of 6.7% (equivalent to an average blood glucose level of approximately 7.6 mmol/l [41]), indicates satisfactory metabolic control for most of the patients at follow-up. The clinical characteristics of these CSII patients were similar to those of a comparable non-diabetic population in Britain [42] except for plasma glucose. No deaths occurred in our study compared to 0.009 to 0.04 deaths per patient-year on CSII, as reported by others [17, 43]. These favourable results may have been promoted by several factors:

1. The participants in this study were in fairly good control with multiple injection therapy [28] prior to initiation of CSII, reflected by the mean HbA_{1c} value of 7.7%.
2. All of the patients in our study were adults with a mean of 14 years experience in diabetes management, who intended to improve their metabolic control/lifestyle by means of CSII.
3. Our patients' frequency of BGSM was rather high (an average of 4 times per day). The patients of Knight et al. performed BGSM on an average of 13 times per week [18]. Schiffrin et al. [44] and Nathan et al. [45] have documented that tight metabolic self-monitoring is essential for successful intensive insulin therapy; thus the effectiveness of intensive insulin therapy (including CSII) appears to decrease with a decreased frequency of BGSM and insulin dose adjustment [46, 47].

Our patients experienced DKA with an annual frequency of 0.14 per patient year, whereas the group of Peden et al. [48] reported 0.22 DKA per patient-year, and the Kroc Collaborative Study group observed approximately 0.4 DKA per patient-year [12]. Note that the incidence of DKA during conventional insulin injection therapy may range from 0.008 DKA per patient year [49] to 0.28 DKA per patient-year [43]. As we have previously shown in unselected Type 1 diabetic patients on insulin injection therapy [29], the rate of DKA depends primarily on the standards of diabetes education and self-care. In that study the annual rate of severe DKA (defined as hyperglycaemia plus clinical signs of ketoacidosis, an arterial pH value of < 7.3, and hospital treatment) was reduced to nearly zero by improved diabetes self care [29]. As this was not achieved in the present study with CSII-treated patients, CSII appears to carry a particular risk for DKA.

The underlying cause of this side effect has recently been identified as a reduced tolerance for the interruption of CSII. Due to the relatively small amount of insulin deposited in the subcutaneous tissue during CSII, relevant insulin deficiency may develop only 3-4 h after cessation of the insulin infusion [50-53]. On the other hand, CSII functions with the least possible peripheral (hyper-)insulinaemia [25, 30] and with overall reduced insulin dosages compared to injection treatment [5-7]; hence, an accidental interruption of CSII can be quite detrimental.

Disabling hypoglycaemia was observed at an annual rate of 0.10 DH per patient. This rate is in agreement with previous reports ranging from 0.09 DH per patient year [16] to 0.13 DH per patient year [13], and 0.19 DH per patient year as reported by our group after observation of the first 46 patient years of CSII [9]. Note that the incidence of DH during conventional insulin injection treatment is similar (ranging from 0.16 to 0.4 per patient year as reported by Home et al. [54]).

However, the incidence of 'severe hypoglycaemia' in this study was substantially lower than the incidence of severe hypoglycaemic reactions as reported for the intervention group (i.e. 0.54 per patient year) at comparable degrees of glycaemic control in the DCCT [35].

Finally, there is a relatively high incidence of infected infusion sites in our study which is explained by the fact that our patients were advised to use topical dis-

infectant prior to insertion of the needle only after 1986 [27]. Since then, the rate of serious infections has declined substantially (unpublished observations).

To compare the outcome of CSII at different levels of glycaemic control, patients were grouped according to their HbA_{1c} value [55, 67]. Because the degree of glycaemic control as obtained by each individual patient may remain fairly constant over a long period of time [57-59], we took the HbA_{1c} at follow-up as representative of the individually achieved degree of diabetes control.

Fourteen percent of the patients were controlled with HbA_{1c} values within 2 standard deviations from the mean normal value, and 38% of the patients had HbA_{1c} values below 6.25%. This is about twice the proportion of Type 1 diabetic patients with a similar degree of diabetic control under traditional treatment, both 10 years ago [60] and at present [55].

Slightly supranormal HbA_{1c} levels (i.e. *excellent control*, HbA_{1c} 5.6-6.25%) in this study was associated with a lower incidence of DH (0.147 DH per patient-year) compared to normal HbA_{1c} (i.e. *normal metabolic control*, $HbA_{1c} < 5.6\%$, 0.242 DH per patient-year). Although a statistical significance for this difference could not be documented, these results seem to suggest that a complete normalisation of HbA_{1c} may represent a risk, amongst others, of DH, and therefore should be recommended only under certain conditions as a target of insulin therapy for Type 1 diabetic patients.

Pending the documentation of long-term benefits of normal vs. slightly supranormal HbA_{1c} levels, striving for a degree of glycaemic control equivalent to the so-called "impaired glucose tolerance" with HbA_{1c} levels between 5.6 and 6.25% (37) and average glycaemia up to 6.8 mmol/l (41,61) may be justified according to Unger [62], except during pregnancy. Such a policy might possibly reduce the risk of disabling hypoglycaemia without introducing a significant risk of microangiopathic diabetic late complications [37, 61].

In conclusion, the present results indicate that under the policies of this diabetes centre, CSII was maintained during a mean of 4.5 years by a majority (83%) of experienced adult Type 1 diabetic patients. At a mean HbA_{1c} of 6.7% the metabolic control of most of these patients was very satisfactory and compares favourably with the results achieved in similar follow-up studies on the quality of care in Type 1 diabetic patients under the conditions of intensified insulin therapies.

Acknowledgements. We are indebted to Dr. Gabriele E. Sonnenberg, Milwaukee, USA, who was instrumental in the organisation of our CSII program until 1986. The dedicated cooperation of the former diabetes nurses Mrs. Astrid Weinrebe and Mr. Michael Brormann during the course of these studies and the financial support of the Peter Klöckner Foundation, Duisburg, FRG, are gratefully acknowledged.

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Received: 7 December 1988
and in revised form: 30 March 1989

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