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Continuous intraperitoneal insulin infusion in the treatment of type 1 diabetes mellitus

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CHAPTER 3

Glycaemic control, quality of life and treat- ment satisfaction after 6 years intraperitoneal insulin infusion with an implantable pump

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Abstract

INTRODUCTION

Continuous intraperitoneal insulin infusion (CIPII) with an implantable pump is a treatment option for selected patients with type 1 diabetes mellitus (T1DM). Aim of the present study was to describe the long-term course of glycaemic control, complications, quality of life (QoL) and treatment satisfaction among T1DM patients treated with CIPII.

PATIENTS AND METHODS

Nineteen patients that participated in a randomized cross-over trial comparing CIPII and subcutaneous (SC) therapy in 2006 were followed until 2012. Laboratory, continuous glucose monitoring, QoL and treatment satisfaction measurements were performed at the start of the study, the end of the SC-, the end of the CIPII treatment phase in 2006 and during CIPII therapy in 2012. Linear mixed models were used to calculate estimated values and to test differences between the moments in time.

RESULTS

In 2012, more time was spent in hyperglycaemia than after the CIPII treatment phase in 2006: 37% (95% confidence interval (CI) 29, 44) versus 55% (95% CI 48, 63) with a mean difference of 19.8% (95% CI 3.0, 36.6). HbA1c was 65 mmol/mol (95% CI 60, 71) at the end of the SC treatment phase in 2006, 58 mmol/mol (95% CI 53, 64) at the end of the CIPII treatment phase and 65 mmol/mol (95% CI 60, 71) in 2012, respectively ($p > 0.05$). In 2012, the median number of grade 2 hypoglycaemic events per week (1 (95% CI 0, 2)) was still significantly lower than during prior SC therapy (3 (95% CI 2, 4)): mean change -1.8 (95% CI -3.4, -0.4). Treatment satisfaction with CIPII was better than with SC insulin therapy and QoL remained stable. Pump or catheter dysfunction of the necessitated re-operation in 7 patients. No mortality was reported.

CONCLUSIONS

After 6 years of CIPII treatment, glycaemic regulation is stable and the number of hypoglycaemic events decreased as compared to prior SC insulin therapy. Treatment satisfaction with CIPII is superior to SC insulin therapy, QoL is stable and complications are scarce. CIPII is a safe and effective treatment option for selected patients with T1DM, also on longer term.

Introduction

The mainstay of type 1 diabetes mellitus (T1DM) treatment consists of subcutaneous (SC) insulin administration using multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) with an externally placed pump. Although most patients achieve acceptable glycaemic control using MDI or CSII, a relatively small group of patients fails to reach adequate glycaemic control, have frequent hypoglycaemic episodes or SC insulin resistance, despite intensive SC insulin therapy. For these patients, continuous intraperitoneal insulin infusion (CIPII) with an implantable pump is a treatment option ¹.

With intraperitoneal administration, insulin is better absorbed and allows blood glucose levels to return to baseline values more rapidly with more predictable insulin profiles compared to SC insulin administration ^{2,3}. The higher hepatic uptake of insulin with CIPII mitigates peripheral plasma insulin concentrations compared to SC administration ^{3,4}. Other possible effects include improvement of the impaired glucagon and hepatic glucose production in response to hypoglycaemia through alleviation of peripheral hyperinsulinaemia ⁵.

In 2006, a randomized, cross-over study was performed at our centre to investigate the effects of CIPII on the risk of hypoglycaemia, compared to intensive SC insulin treatment, both for a six-month period. Glycaemic control, quality of life (QoL) and treatment satisfaction improved during CIPII treatment as compared to SC insulin administration and there was no reduction or increase in hypoglycaemic events ^{6,7}. After the study all participants chose to continue CIPII.

Aim of the current analysis is to investigate long-term glycaemic control, QoL, treatment satisfaction and complications among these patients with T1DM, treated with CIPII.

Patients and methods

STUDY POPULATION

Twenty three patients with T1DM, low fasting C-peptide concentrations (<0.2 nmol/l) and intermediate or poor glycaemic control, defined as HbA1c \geq 58 mmol/mol and/or \geq 5 incidents of hypoglycaemia (<4.0 mmol/l) per week, who were aged 18–70 years and treated with SC insulin, were included in the cross-over study in 2006. The exclusion criteria were: impaired renal function (plasma creatinine \geq 150 μ mol/l or glomerular filtration rate \leq 50ml/min), cardiac problems (unstable angina or myocardial infarction within the previous 12 months

or New York Heart Association class III or IV congestive heart failure), cognitive impairment, current or past psychiatric treatment for schizophrenia, cognitive or bipolar disorder, current use or oral corticosteroids or suffering from a condition which necessitated oral or systemic corticosteroids use more than once in the previous 12 months, substance abuse, other than nicotine, current pregnancy or plans to become pregnant during the trial, plans to engage in activities that require going >25 feet below sea level. After the cross-over study all patients chose to continue CIPII with an implantable pump (Minimed Insulin Pump).

STUDY DESIGN

The previous study (NCT00286962) started in 2006, had an open-label, randomized cross-over design and was performed at Isala (Zwolle, the Netherlands). The study consisted of 4 phases: the qualification phase, the first treatment phase, the crossover phase, and the second treatment phase. After a 3-month qualification phase, patients were randomly allocated to one of two groups, which differed only in the sequence of the two therapies. Between both treatment phases of 6 months, a crossover phase of 4 weeks was instituted to minimize the carryover effects of CIPII. The results of this study were reported previously and showed a significant decrease in HbA1c, with more time spent in euglycaemia and without a change in hypoglycaemic events with CIPII as compared to SC insulin therapy. In addition, QoL and treatment satisfaction improved with CIPII ^{6,7}. Follow-up measurements for the present analysis were performed in December 2012 until March 2013.

PROCEDURES AND METHODS

At the start of the 2006 cross-over study, 3 patients were on MDI and 20 on CSII. During the SC treatment phase in the 2006 study, SC insulin was delivered with either MDI or CSII, according to what was used prior to the study. Patients treated with MDI continued to use their own insulin regime, i.e. rapid-acting insulin analogues before meals and a daily dose of long-acting insulin. Patients treated with CSII used rapid acting insulin analogues. During the crossover phase insulin was administered SC. If the subject was using more than 40 IU of SC insulin per day prior to starting the CIPII phase of the study, his or her starting dose was set at 90% of the prior SC dose. Subjects using less than 40 IU of SC insulin received a starting dose of 80% of the prior SC dose. Initially the dose was equally divided between a basal rate (50%) and a bolus before meals ⁸.

In 2006-2007, the CIPII pump was implanted under general anaesthesia at the start of the CIPII phase in all subjects. Insulin (U-400 HOE 21PH, semi synthetic human insulin of porcine origin, trade name: Insuplant[®] Hoechst, Frankfurt, Germany, nowadays Sanofi-Aventis) was

administered with the implantable pump. Since there were no batches left of the U400 semi synthetic human insulin, a new human recombinant insulin (400 IU/ml; human insulin of E. Coli origin, trade name: Insuman Implantable®, Sanofi-Aventis) was used from 2010 onwards. Between 2006 and 2012, all patients received standard care at our outpatient clinic which consisted of insulin refills every 6-12 weeks and a rinse procedure with NaOH was performed every 9 months or in case of insulin underdelivery. The insulin pump, implantation, insulin dosage and refill procedures have been described in more detail previously^{8,9}.

MEASUREMENTS

In order to yield information about the long-term impact of CIPII on glycaemic control in comparison to that on SC insulin therapy, we compared data derived from the measurements in 2012/2013 (referred to as “2012 study”) with data from the start of the 2006 study, the end of the SC-, the end of the CIPII phase of the 2006 cross-over study.

Demographic and clinical parameters included smoking and alcohol habits, year of diagnosis of diabetes, presence of complications, any comorbidity, height and weight, daily insulin dose, number of self-reported hypoglycaemic events grade 1 (<4.0 mmol/l) and grade 2 (<3.5 mmol/l) during the last 7 days. The HbA1c level was measured with a Primus Ultra2 system using high-performance liquid chromatography (reference value 20-42 mmol/mol). In addition, 5- to 7-day 24-hours interstitial glucose profiles were recorded with a continuous glucose monitoring (CGM) system (iPro2, Medtronic, Northridge, CA, USA). Time spent in the hypoglycaemic range was defined as the percentage of CGM recordings <4.0 mmol/l, time spent in euglycaemic range was defined as the percentage of CGM recordings from 4.0 to 10.0 mmol/l, and time spent in hyperglycaemic range was defined as the percentage of CGM recordings >10.0 mmol/l.

For QoL assessment, the 36-item short-form health survey (SF-36) and the World Health Organization-Five Well-Being Index (WHO-5) questionnaires were used. The SF-36 is a widely used, generic questionnaire with 36 items involving eight subscales and a physical and mental component summary (PCS and MCS, respectively). Scale scores range from 0 to 100, with higher scores indicating better QoL^{10,11}. The WHO-5 is designed to measure positive well-being and is reported to be better in identifying depression than the MCS^{12,13}. It consists of five items with a total score ranging from 0 to 100. A total score below 50 or an answer of “0 or 1” on a single item suggests poor emotional well-being¹⁴. Treatment satisfaction was measured with the Diabetes Treatment Satisfaction Questionnaire (DTSQ). All eight items are scored on a 7-point scale. Two items assess perceived frequency of hyperglycaemia and hypoglycaemia, and six items comprise the treatment satisfaction scale, with higher scores indicating higher satisfaction (range 0 to 36)¹⁵.

STATISTICAL ANALYSIS

Descriptive summaries included the mean with standard deviation (SD) for normally distributed variables and the median with the interquartile range [25th-75th percentile] for other variables. Q-Q plots were used to determine if the tested variable had a normal distribution or not. Time variables, such as times spent in the different glycaemic states, are presented as absolute values. Linear mixed models with Bonferroni correction were used to calculate and to test differences in time. Estimated values and estimated differences, calculated with linear mixed models, are reported. All observed values are presented in Appendix 1. All statistical analysis were performed with SPSS software (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). A two-sided significance level of 0.05 was considered statistically significant.

ETHICAL CONSIDERATIONS

Studies were performed in accordance with the Declaration of Helsinki. For this study, informed consent was obtained from all patients in 2006 as well as in 2012. Approval by the medical ethics committee of the Isala (Zwolle, the Netherlands) was given for the crossover study in 2006 and the follow-up measurements in 2012.

Results

PATIENTS

Of 23 patients who participated in the previous cross-over study, 22 were still treated with CIPII in 2012. One patient stopped CIPII treatment due to neuropathic pains. The patient believed the implanted pump caused this pain. Two female patients were excluded from the current analysis: 1 due to chronic prednisolone use for myasthenia gravis and 1 due to participation in an in vitro fertilization program. One patient refused participation. Therefore, 19 patients (53% male) are included in the present analysis, with a mean age of 45 (10) years and a diabetes duration 23 [16, 33] years at the start of the 2006 study. Four of these patients are current smokers.

CLINICAL PARAMETERS

The estimated values of the clinical parameters and comparisons between the start of the 2006 study, the end of the SC-, the end of the CIPII treatment phase and the start of the present 2012 study, 6 (0.4) years later, are presented in Table 1. Systolic blood pressure, BMI, cholesterol and the insulin dose remained stable over time. Two patients were diagnosed with neuropathy, one

with retinopathy and one with a macrovascular complication (occlusion of the femoral artery). There were no new cases of nephropathy.

GLYCAEMIC PARAMETERS

As shown in Table 1, the mean estimated HbA_{1c} in 2012 was 65 (95% confidence interval (CI) 60, 71) mmol/mol and was not significantly different from the HbA_{1c} at the start of the 2006 study: 70 (95% CI 64, 75) mmol/mol, with a mean estimated change of -4.5 mmol/mol (95% CI -14.9, 5.9). Although there was a tendency to rise, the HbA_{1c} in 2012 did not differ significantly from the HbA_{1c} at the end of the SC phase (-0.1 mmol/mol 95% CI -10.5, 10.3) and the end of the CIPII phase (7.1 mmol/mol 95% CI -3.3, 17.5) of the 2006 study.

The number of grade 2 hypoglycaemic events per week decreased from 3 (95% CI 2, 4), at the start and at the end of the SC therapy phase of the 2006 study, to 1 (95% CI 0, 2) event per week in 2012. In 2012, compared with the start of the 2006 study the mean change was -1.8 events per week (95% CI -3.4, -0.4) and compared with the end of SC therapy phase the mean change was -1.9 (95% CI -3.5, -0.4). More time was spent in hyperglycaemia during CGM measurements in 2012 than at the end of the CIPII phase in 2006: mean change 19.8 (95% CI 3.0, 36.6).

Percentage time spent in euglycaemia with CIPII in 2012 was less than at the end of the CIPII phase of the 2006 study: mean change -18.7% (95% CI -33.3, -4.1).

QOL AND TREATMENT SATISFACTION

As shown in Table 2, none of the SF-36 subscales and component scores changed over time.

The WHO-5 scores in 2012 remained stable over the years with CIPII. In 2012, 8 patients had a poor emotional well-being according to the WHO-5 questionnaire, compared to 9 at the end of the SC phase and 2 at the end of the CIPII study phase. The treatment satisfaction remained significantly higher with CIPII than with SC insulin: the mean difference between 2012 and the start of the 2006 study was 8.3 (95% CI 2.3, 14.3) and between 2012 and the end of the SC phase was 8.4 (95% CI 2.4, 14.3). The perceived hyperglycaemia score of the DTSQ was higher in 2012 than at the end of the 2006 CIPII therapy phase with a difference of 1.5 (95% CI 0.2, 2.7).

DEVICE COMPLICATIONS

After a mean duration of 5 (1) years, 3 cases of pump dysfunction and 3 cases of (expected) battery end-of-life necessitated replacement of the pump. In 3 patients a laparoscopic procedure was performed to replace the catheter and in 1 patient a laparoscopic operation was necessary to remove a fibrin plug from the tip of the catheter. The mean duration of hospital admission for the 10 patients who experienced any pump related issue (including planned replacement due to battery end-of-life) was 0.6 [0, 1] days per year. No mortality was reported.

Discussion

After 6 years of treatment with CIPII, HbA_{1c} leveled with the value these T1DM patients had during intensive SC therapy, prior to starting CIPII. Nevertheless, patients experienced significant less grade 2 hypoglycaemic events and remained much more satisfied with CIPII compared to the SC treatment.

During the previous cross-over trial in which CIPII was commenced there was a significant decrease in HbA_{1c} compared to the SC treatment phase from 70 to 58 mmol/mol. Compared to the SC treatment phase, the decrease in that study was significantly greater with CIPII with a mean difference of 8.4 mmol/mol. During the follow-up period described in the present study HbA_{1c} stabilized at a level of 65 mmol/mol, which was not different to the levels prior and shortly after starting CIPII 6 years before. Several studies have described the effect of CIPII, as compared to SC insulin therapy, on glycaemic control. In all 3 short-term randomized studies, HbA_{1c} improved with CIPII^{6,16,17}. In contrast to the findings in the present study, HbA_{1c} improvement persisted over the years in subsequent long-term observational studies. Nevertheless, follow-up duration (45 days to 7.3 years) varied substantially between studies and, importantly, not all patients in those studies had intermediately or poorly controlled T1DM (HbA_{1c} ranging from 63 to 83 mmol/mol)^{18–24}.

In accordance with previous studies, the number of grade 2 hypoglycaemic events decreased during CIPII in the present cohort as compared to prior SC therapy^{16,20,25}. This may well be the result of a slightly more hyperglycaemic profile. Although speculative, the restoration of the portal to peripheral insulin gradient with CIPII treatment, known to improve glucagon secretion and hepatic glucose production in response to hypoglycaemia, may also help to explain this finding^{5,26}.

The HbA_{1c} course in the current cohort may be partly explained by the effect of being under strict study conditions during the cross-over study, which diminishes after the end of the study. Several other explanations may be taken into account. First, complications of CIPII may also have a negative influence on glycaemic regulation. Second, it should be mentioned that from 2010 onwards all CIPII patients switched to another insulin (Insuman[®] Implantable 400 IU/mL) because the previous insulin batch (U-400 HOE 21PH, Insuplant[®] 400 IU/mL) was no longer available. The effect of the change in insulin formulation remains to be determined from an on-going study (clinical trials identifier NCT01194882).

TABLE 1 Clinical and glycaemic parameters.

	Start 2006 study (A)		End SC phase (B)		End CIPII phase (C)		2012 study (D)		D vs. A	D vs. B	D vs. C
Clinical parameters											
SBP (mmHg)	141 (133, 150)	135 (126, 143)	139 (130, 147)	140 (131, 149)	-1.1 (-17.6, 15.5)	5.5 (-11.0, 22.0)	1.3 (-15.2, 17.9)				
BMI (kg/m ²)	26 (24, 29)	27 (24, 29)	28 (25, 30)	26 (24, 29)	-0.4 (-4.9, 4.1)	-0.2 (-5.3, 4.9)	-1.2 (-6.1, 3.7)				
Total cholesterol	4.8 (4.5, 5.2)	4.7 (4.3, 5.1)	4.5 (4.1, 4.9)	4.8 (4.4, 5.2)	-0.1 (-0.9, 0.7)	0.0 (-0.7, 0.8)	-0.2 (-0.5, 1.0)				
HDL cholesterol	1.8 (1.6, 2.0)	1.8 (1.5, 2.0)	1.6 (1.3, 1.8)	1.7 (1.4, 1.9)	-0.1 (-0.6, 0.3)	-0.1 (-0.6, 0.4)	0.1 (-0.3, 0.6)				
LDL cholesterol	2.6 (2.3, 3.0)	2.5 (2.2, 2.8)	2.4 (2.1, 2.7)	2.8 (2.5, 3.1)	0.2 (-0.4, 0.8)	0.3 (-0.3, 0.9)	0.4 (-0.2, 1.1)				
Triglycerides	0.9 (0.7, 1.2)	1.1 (0.8, 1.3)	1.3 (1.0, 1.5)	1.0 (0.7, 1.3)	-0.1 (-0.5, 0.6)	-0.1 (-0.6, 0.5)	-0.3 (-0.8, 0.3)				
Total insulin dose (IU/day)	19 (13, 24)	25 (20, 31)	20 (15, 25)	20 (15, 26)	8.2 (-18.3, 34.7)	8.2 (-17.6, 33.9)	6.1 (-19.7, 31.8)				
Basal insulin dose (IU/day)	35 (24, 45)	32 (22, 43)	35 (25, 46)	44 (34, 55)	9.6 (-10.6, 29.8)	12.0 (-8.1, 32.2)	8.5 (-11.7, 28.7)				
Bolus insulin dose (IU/day)	54 (40, 67)	58 (44, 71)	56 (42, 69)	65 (51, 78)	1.4 (-8.9, 11.7)	-5.1 (-15.3, 5.2)	0.4 (-9.9, 10.7)				
Glycaemic parameters											
HbA1c (mmol/mol)	70 (64, 75)	65 (60, 71)	58 (53, 64)	65 (60, 71)	-4.5 (-14.9, 5.9)	-0.1 (-10.5, 10.3)	7.1 (-3.3, 17.5)				
Hypoglycaemia grade 1†	4 (3, 6)	4 (3, 6)	4 (2, 5)	3 (1, 4)	-1.8 (-4.2, 0.7)	-1.7 (-4.2, 0.8)	-1.1 (-3.6, 1.4)				
Hypoglycaemia grade 2‡	3 (2, 4)	3 (2, 4)	2 (2, 3)	1 (0, 2)	-1.8 (-3.4, -0.4)*	-1.9 (-3.5, -0.4)*	-1.4 (-3.0, 0.1)				
Time spent in hypoglycaemia (%)	8 (5, 11)	8 (5, 11)	6 (3, 9)	5 (2, 7)	-3.7 (-9.3, 1.9)	-3.6 (-9.2, 2.0)	-1.1 (-6.7, 4.5)				
Time spent in hyperglycaemia (%)	45 (36, 54)	47 (38, 56)	39 (30, 48)	59 (50, 68)	13.7 (-3.1, 30.5)	12.0 (-4.8, 28.8)	19.8 (3.0, 36.6)*				
Time spent in euglycaemia (%)	47 (39, 54)	45 (38, 53)	55 (48, 63)	37 (29, 44)	-10.0 (-24.6, 4.6)	-8.4 (-23.0, 6.2)	-18.7 (-33.3, -4.1)*				

Estimated values and differences are reported. Data are presented as estimated mean (95% CI) or mean change (95% CI). Numbers may not add up due to rounding. Abbreviations BMI, body mass index, CIPII, continuous intraperitoneal insulin infusion, SBP, systolic blood pressure, SC, subcutaneous, † Defined as the number of blood glucose values <4.0 mmol/l per week. ‡ Defined as the number of blood glucose values <3.5 mmol/l per week. *p<0.05.

TABLE 2 QoL and treatment satisfaction.

	Start 2006 study (A)	End SC phase (B)	End CIPII phase (C)	2012 study (D)	D vs. A	D vs. B	D vs. C
SF-36 subscales							
Physical functioning	76 (66, 86)	69 (59, 79)	81 (71, 91)	76 (65, 86)	-0.3 (-19.7, 19.1)	7.4 (-12.1, 26.8)	-5.3 (-24.7, 14.1)
Social functioning	68 (53, 76)	65 (53, 76)	77 (66, 88)	74 (63, 85)	6.6 (-14.7, 27.8)	9.9 (-11.4, 31.2)	-2.6 (-32.9, 18.6)
Role limitations-physical	38 (17, 59)	42 (21, 63)	66 (45, 87)	57 (36, 78)	18.4 (-22.0, 58.8)	14.5 (-26.0, 54.9)	-9.2 (-49.6, 31.2)
Role limitations-emotional	68 (50, 87)	68 (50, 87)	86 (67, 100)	77 (58, 96)	8.8 (-27.3, 44.8)	8.8 (-27.3, 44.8)	-8.8 (-44.8, 27.3)
Mental health	70 (60, 79)	67 (58, 77)	77 (68, 87)	79 (70, 89)	9.6 (-8.1, 27.4)	12.0 (-5.8, 29.7)	2.1 (-15.7, 19.8)
Vitality	48 (39, 58)	43 (34, 71)	62 (52, 71)	58 (49, 67)	9.5 (-7.9, 26.9)	15.3 (-2.2, 32.7)	-4.5 (-32.9, 12.8)
Bodily pain	64 (52, 75)	64 (53, 76)	66 (54, 77)	67 (56, 78)	3.3 (-18.5, 25.0)	2.6 (-19.2, 24.3)	1.4 (-20.4, 23.1)
General health	41 (32, 50)	46 (37, 54)	56 (47, 64)	48 (38, 56)	6.5 (-10.1, 23.1)	1.7 (-14.9, 18.3)	-8.0 (-24.7, 8.6)
SF-36 component scores							
Mental component score	59 (50, 68)	58 (49, 67)	72 (63, 81)	67 (58, 76)	8.2 (-9.1, 25.5)	9.5 (-7.7, 26.8)	-4.4 (-21.6, 12.9)
Physical component score	56 (46, 65)	55 (45, 64)	68 (58, 77)	63 (54, 73)	7.3 (-10.9, 25.6)	8.5 (-9.7, 26.8)	-4.7 (-23.0, 13.5)
WHO-5 score	49 (39, 59)	47 (37, 57)	69 (59, 79)	60 (50, 70)	10.5 (-9.0, 30.0)	12.6 (-6.9, 32.1)	-9.2 (-28.8, 10.2)
DTSQ							
Perceived hyperglycaemia score	3 (2, 4)	4 (3, 5)	3 (2, 3)	3 (2, 4)	-1.1 (-2.4, 0.1)	-0.9 (-2.1, 0.3)	1.5 (0.2, 2.7)*
Perceived hypoglycaemia score	5 (4, 6)	5 (4, 5)	2 (2, 3)	4 (3, 5)	-0.4 (-2.0, 1.2)	-0.8 (-2.4, 0.8)	0.3 (-1.3, 1.9)
Total score	24 (21, 27)	24 (21, 27)	33 (30, 36)	33 (29, 36)	8.3 (2.3, 14.3)*	8.4 (2.4, 14.3)*	-0.3 (-6.3, 5.7)

Estimated values and differences are reported. Data are presented as estimated mean (95% CI) or mean change (95% CI). Numbers may not add up due to rounding. Abbreviations: DTSQ; diabetes treatment satisfaction questionnaire; CIPII; continuous intraperitoneal insulin infusion; SC; subcutaneous; SF-36; 36-item short-form health survey; WHO-5; world health organization-five well-being index. *p<0.05.

The switch from SC insulin to CIPII increases QoL, which stabilizes over time^{7,20}. In the present study the level of QoL among CIPII treated subjects perpetuated. Nevertheless, as found in other studies and emphasized by the fact that 42% of all patients had a WHO-5 score indicating poor emotional well-being, the QoL of these individuals remains poor^{1,19,20}. We found the SF-36 subscales role-physical and vitality to be comparable to patients with a minor (uncomplicated) chronic disease and the other subscales similar to patients with complicated diabetes or complicated coronary artery disease²⁷. Still, it is likely that the short duration of hospital admissions found in the present study (<1 day per year), compared to 45 days per year before implantation of the pump previously described in a similar population, positively influence QoL and treatment satisfaction¹⁹.

Since CIPII is used as a last treatment option in the Netherlands, the population in the present study is complex, strictly selected and has a small size. On the other hand, this limitation reflects general practice nowadays where CIPII is limited to a small number of patients in a small number of centers. Furthermore, when interpreting the comparisons between CIPII and previous SC therapy made in this study one should take differences in treatment periods (e.g. a duration of 6 months of the SC phase during a controlled study versus 6.4 years of subsequent CIPII therapy) into account. Prospective, long-term and large-scale studies with respect to glycaemic control, QoL and cost-effectiveness to compare CIPII and SC therapy for T1DM are imperative.

Conclusions

Taken together, the stable QoL, increased treatment satisfaction, little time spent in hospital and stable HbA1c combined with a decrease in grade 2 hypoglycaemic events as compared to previous SC therapy underlines the clinical observation that CIPII is a valuable treatment option for selected patients with T1DM, also on longer term.

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APPENDIX 1 Observed values at the different moments in time.

	Start 2006 study	End SC phase	End CIPII phase	2012 study
Clinical parameters				
SBP (mmHg)	141 (21)	135 (18)	139 (19)	140 (17)
BMI (kg/m ²)	26.6 (5.2)	26.5 (4.8)	27.5 (5.2)	27.5 (4.5)
Total cholesterol	4.8 (0.8)	4.7 (0.9)	4.5 (0.9)	4.8 (1.0)
HDL cholesterol	1.8 (0.5)	1.7 (0.5)	1.6 (0.5)	1.7 (0.6)
LDL cholesterol	2.7 (0.7)	2.5 (0.7)	2.4 (0.6)	2.8 (0.8)
Triglycerides	0.9 (0.4)	1.1 (0.6)	1.2 (0.8)	1.0 (0.5)
Total insulin dose [IU/day]	50 [35, 75]	50 [40, 68]	49 [35, 70]	57 [46, 74]
Basal insulin dose [IU/day]	28 [22, 31]	26 [13, 37]	30 [20, 52]	37 [26, 60]
Bolus insulin dose [IU/day]	16 [10, 25]	21 [13, 37]	16 [13, 30]	17 [13, 28]
Glycaemic parameters				
HbA1c (mmol/mol)	70 (12)	65 (13)	58 (9)	65 (13)
Hypoglycaemia grade 1 †	4 (2, 5)	4 (1, 7)	3 (2, 5)	2 (0, 3)
Hypoglycaemia grade 2 ‡	3 (1, 4)	3 (1, 4)	2 (1, 3)	1 (0, 2)
Time in hypoglycaemia (%)	8 (7)	8 (8)	6 (6)	5 (5)
Time in hyperglycaemia (%)	45 (16)	47 (20)	39 (19)	59 (20)
Time in euglycaemia (%)	47 (12)	45 (16)	55 (18)	36 (19)
SF-36				
Physical functioning	76 (20)	69 (24)	81 (21)	76 (23)
Social functioning	68 (21)	65 (29)	77 (25)	74 (21)
Role limitations-physical	38 (11)	42 (11)	66 (11)	57 (11)
Role limitations-emotional	68 (10)	68 (9)	86 (9)	77 (9)
Mental health	70 (24)	67 (22)	77 (17)	79 (17)
Vitality	48 (22)	43 (21)	62 (19)	58 (18)
Bodily pain	64 (25)	64 (29)	66 (23)	67 (21)
General health	41 (18)	46 (21)	56 (19)	48 (17)
Physical component score	56 (18)	55 (24)	69 (20)	63 (21)
Mental component score	59 (20)	58 (22)	72 (19)	67 (17)
WHO-5-score	50 (21)	48 (25)	70 (21)	60 (22)
DSTQ				
Total score	24 (8)	23 (9)	33 (4)	32 (3)
Perceived hypoglycaemia score	3 (2)	4 (2)	3 (2)	3 (1)
Perceived hyperglycaemia score	5 (1)	5 (1)	2 (2)	4 (2)

Data are presented as mean (SD), median [IQR]. Observed values are reported. Abbreviations BMI; body mass index, CIPII; continuous intra-peritoneal insulin infusion, SBP; systolic blood pressure, SC; subcutaneous. *p<0.05. † Defined as a number of blood glucose value <4.0 mmol/l per week. ‡ Defined as a number of blood glucose value <3.5 mmol/l per week.