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Glycaemic control, health status and treatment satisfaction with continuous intraperitoneal insulin infusion

S.J.J. Logtenberg*, E. van Ballegooie, H. Israël-Bultman, A. van Linde, H.J.G. Bilo

Department of Internal Medicine, Isala Clinics, P.O. Box 10400, 8000 GK Zwolle, the Netherlands,
*corresponding author: tel.: +31 (0)38-424 46 48; fax: +31 (0)38-424 33 67;
e-mail: s.j.j.logtenberg@isala.nl.

ABSTRACT

Background: Continuous intraperitoneal insulin infusion (CIPII) has been in use for over 20 years. High costs and technical problems have prevented its widespread use. In the Netherlands, the Isala Clinics in Zwolle is the centre with the most extensive experience with CIPII. Its use is aimed at improving glycaemic control with less hypoglycaemic events, and thus improving quality of life in patients with poorly controlled diabetes despite intensified insulin treatment. Our aim was to assess glycaemic control, health status and treatment satisfaction in subjects treated with CIPII within the Isala Clinics.

Methods: Retrospective longitudinal analysis of clinical data in 48 patients started on CIPII between 1983 and 2005. HbA_{1c} at baseline, after one year, and at present assessment or at the end of pump use were applicable. Cross-sectional assessment of health status, well-being and treatment satisfaction was carried out.

Results: Of 48 patients, 33 were treated with CIPII at the moment of assessment. Five patients died whilst on CIPII; four from diabetes-related causes, none from hypoglycaemia. HbA_{1c} decreased significantly from 9.7 to 8.8% after one year, to 8.6% at long-term follow-up; $p<0.01$. Less hypoglycaemic events were reported. Short-Form 12-Item Health Survey (SF-12) scores were 37.4 and 47.2 (range 0-100), the Well-Being Index (WHO-5) score was 52.7 (range 0-100) and median treatment satisfaction score was 32 (range 0-36).

Conclusion: CIPII leads to improved glycaemic control with less self-reported hypoglycaemic events in patients with poorly controlled diabetes. Treatment satisfaction is high. Mental health status and well-being scores are low, however.

KEYWORDS

Diabetes mellitus, intensive insulin treatment, CIPII, quality of life

INTRODUCTION

Continuous intraperitoneal insulin infusion (CIPII) has been a promising treatment for diabetes mellitus for the last 20 years. The use of the peritoneal cavity rather than subcutaneous tissue for insulin administration may explain the beneficial effect on diabetes control and the lower risk of hypoglycaemia from this treatment modality. Insulin delivered through the intraperitoneal (IP) route is better absorbed and allows blood glucose values to return to baseline values more rapidly with more predictable insulin profiles compared with subcutaneous injections of regular or long-acting insulin.[1,2] Furthermore, much of the IP insulin is absorbed by the portal system, mimicking the physiological situation and resulting in higher hepatic uptake and thus lower peripheral plasma insulin concentrations compared with systemic administration.[3] Other possible effects include improvement of the impaired glucagon secretion and hepatic glucose production in response to hypoglycaemia through alleviation of peripheral hyperinsulinaemia.[4] These properties may have a favourable impact on hypoglycaemia, thus being of importance in diminishing risk in subjects experiencing hypoglycaemia unawareness.

Research with IP delivery of insulin in type 1 and type 2 diabetic subjects has shown that it is an appropriate therapy that allows subjects to achieve acceptable glycaemic control without increasing the inherent risk of severe

hypoglycaemia observed when intensive insulin treatment is pursued.[5-10]

Living with diabetes has a major effect on health-related quality of life and well-being, not only because it is a chronic disease but also because diabetes-related tasks have to be performed every day.[11] Partly because of this, almost one in three people with diabetes suffer from symptoms of depression.[12] This and other psychosocial factors are often stronger predictors of medical outcomes such as hospitalisation and mortality than are measures such as HbA_{1c} or body mass index (BMI).[13]
It is hypothesised that CIPII can have a positive influence on quality of life, not only because it can result in better glycaemic control and less hypoglycaemic events, but also because it does not require multiple injections as does subcutaneous insulin delivery by pen, and it does not have the inconvenience of an external pump as is the case with subcutaneous insulin infusion (CSII). Results from clinical trials suggest that CIPII can indeed have a positive effect on health-related quality of life and well-being.[7-9]
Such effects provide the arguments to make IP insulin in theory the most effective and physiological mode of insulin delivery. However, due to technical problems and its high costs it is still not widely used. At this moment the only available implantable pump is the model 2007 from Medtronic/Minimed (Northridge, CA, USA), and though the CE mark approval enables commercial distribution in Europe, there is still no approval by the American Food and Drug Administration.
In the past, system blockades through insulin aggregates and catheter obstructions were the two major problems resulting in underdelivery of insulin.[10,14-15] Due to improvements in the process of preparing the specific insulin used for IP therapy, the occurrence of insulin aggregates has dropped in the recent years.[16]
Haardt *et al.* compared CIPII with multiple subcutaneous injections and reported the direct costs of CIPII as being 2.6 fold higher.[9] These data are from a decade ago, and since then improvements such as longer battery life will probably have reduced costs.

Up until 2001 approximately 1100 pumps were used worldwide, most of them in France.[14] In 2004, 406 patients were treated with CIPII.[17] In the Netherlands CIPII is only considered as a last resort for patients with 'brittle' diabetes who are not responding on multiple daily insulin injections (MDI) or CSII, or in patients with subcutaneous insulin resistance.[18]
The Isala Clinics in Zwolle is the Dutch centre with the most extensive experience with this treatment option. The objective of this report is to describe CIPII regarding glycaemic control, health status and patient satisfaction in this group of patients.

MATERIAL AND METHODS

All patients treated with CIPII and cared for in the Isala Clinics in Zwolle were eligible for the study. Data were collected on glycaemic control, duration of diabetes and data on start and cessation of CIPII from hospital records. Glycaemic control was assessed using HbA_{1c} prior to implantation, one year after implantation and at long-term follow-up.
Patients currently on CIPII and treated in our clinic received a questionnaire by mail. This survey contained questions regarding number of hospital admissions in the previous year, number of self-controls of blood glucose daily, number of hypoglycaemic events in the last four weeks and macrovascular complications. BMI was calculated with self-reported height and weight for all survey respondents and in other cases data from hospital records were used. In addition, we asked about perception regarding glycaemic control and hypoglycaemic events with CIPII as compared with previous insulin treatment. Finally, using self-administered questionnaires, health status and treatment satisfaction were assessed.

Health status, well-being and treatment satisfaction

To measure health status and well-being the Short-Form 12-Item Health Survey (SF-12) and the WHO-5 Well-Being Index (WHO-5) were used.[19,20]
The SF-12 is a generic measure of health status and is derived from the Short-Form 36-Item Health Survey (SF-36). Using scoring algorithms two summary scores can be derived from the SF-12: the Mental Component Summary (MCS) and the Physical Component Summary (PCS).[21] These summary measures are highly correlated with the SF-36 summary measures.[19] Gandek *et al.* reported on the high degree of equivalence observed in ten countries (including the Netherlands) and therefore recommend using the standard scoring algorithms. The PCS and MCS scores have a range of 0 to 100 and were designed to have a mean score of 50 and a standard deviation of 10 in a representative sample of the US population.[22] The SF-12 has been found to be both valid and reliable. Both the SF-36 and the SF-12 are widely used health status measurement tools. This makes comparison of health status of different populations possible.

The WHO-5 is derived from a larger rating scale developed for a World Health Organisation project on quality of life in primary health care.[20] It was designed to measure positive well-being. The WHO-5 is recommended by the WHO as a first step in a two-stage screening process for depression.[20] The WHO-5 consists of five items, whereby every answer is given on a score between 0 and 5, giving a raw score from 0 to 25. To allow comparison with other

scales, the WHO-5 can be transformed to a 0 to 100 scale. A raw score below 13, i.e. score below 50 on the 0 to 100 scale, indicates poor well-being and is considered to be an indicator for depression, which should be confirmed using the Major (ICD-10) Depression Inventory and patient interviews.[23] High reliability and clinical validity of the WHO-5 as a screening instrument of depression and well-being in people with diabetes was found by Shea *et al*.[24]

The Diabetes Treatment Satisfaction Questionnaire (DTSQ) was used to measure satisfaction with treatment.[25] The DTSQ can be applied for both type 1 and type 2 diabetes patients. The questionnaire consists of eight items, all scored on a seven-point scale, ranging from 'very satisfied' (6) to 'very dissatisfied' (0). The DTSQ has three subscales: treatment satisfaction (6 items), perceived frequency of hyperglycaemia (1 item) and perceived frequency of hypoglycaemia (1 item).[25] The DTSQ has been used in Dutch studies.[26,27]

Statistical analysis

The statistical analyses were carried out using SPSS version 12.0.1. Statistical significance was taken at $p<0.05$. Where appropriate, parametric (Student's t) and non-parametric (Mann-Whitney U) tests were used to compare outcome measures. To test the difference in HbA_{1c} and BMI paired samples t-tests were performed.

RESULTS

Forty-eight patients were identified who had received an implantable insulin pump for CIPII in the Isala Clinics in Zwolle, the Netherlands from 1983 up till December 2005. At the time of our study in December 2005, 33 patients were treated with CIPII. Patient characteristics are shown in *table 1*.

Reasons for cessation of CIPII are given in *table 2*. In total 33% (n=5) died while on CIPII, in four cases the cause of death was diabetes related, with kidney failure and heart failure each being the cause of death in two cases. Since cessation of CIPII, four patients died while on other forms of insulin therapy.

The response of patients still on CIPII regarding the questionnaire was high with 30 out of 33 (91%) questionnaires returned.

Glycaemic control

HbA_{1c} at all three study points could be retrieved for 41 out of 48 patients. Patients reported less hypoglycaemic events with CIPII. Mean HbA_{1c} before implantation was 9.7% (SD 1.7). One year after implantation (median 12.0 months, P^{25}-P^{75}: 9.5-14.0) HbA_{1c} had decreased significantly to 8.8% (SD 1.7) ($p=0.004$). This improvement was sustained during long-term follow-up: HbA_{1c} at follow-up after a mean of 6.0 years (median 4.5; P^{25}-P^{75}: 2.3-11.1) was 8.6% (SD 1.6) ($p=0.001$ *vs* baseline).

Table 1. *Patient characteristics*

Characteristic	All patients	Currently on CIPII [1]
n	48	33
Sex (m/f) (*n*)	10/38	7/26
Type of DM (*n*)		
1	41	27
2	6	6
Undetermined	1	-
Age at time of implantation (years)	36.3 (13.1; 13.8 – 60.6)	36.6 (14.4; 13.8 – 60.6)
Diabetes duration at time of implantation (yrs)	17.2 (9.8; 3 – 37)	16.3 (9.1; 3 – 37)
HbA_{1c} (%)	9.7 (1.7; 6.1 – 12.6)[2]	9.9 (1.5; 7.2 – 12.0)[2]
Smoking (%)	25	27
Use of alcohol (%)	49	49

Values are number of patients, mean (SD; range) or percentage of patients; [1]at assessment in fourth quarter of 2005; [2]missing data due to incomplete dataset; DM= diabetes mellitus.

Table 2. *Cessation of CIPII*

Reason for stopping CIPII *	n
Inadequate glycaemic control	4
Pump failure	3
Kidney/pancreas transplantation	2
Recurrent infection of pump	1
Death from diabetes related complications	
Kidney failure	2
Heart failure	2
Death from other cause	1

*** as recorded in hospital records.**

BMI

BMI could be calculated both before and on CIPII for 26 patients. Mean BMI did not increase significantly: 24.4 (SD 4.0) before CIPII to 25.1 (SD 4.3) on CIPII ($p=0.46$; median 3.5 years after implantation, P^{25}-P^{75}: 1.9-12.9).

Self-reported variables

The self-reported variables are shown in *table 3*. Altogether, 73% reported no hospital admissions related to their diabetes in the year preceding the questionnaire. The median number of daily blood glucose measurements was 5 (P^{25}-P^{75}: 4-7). Some 87% perceived a better glycaemic regulation on CIPII as compared with previous insulin treatment modalities, while 67% perceived less hypoglycaemic incidents with CIPII.

Table 3. *Patient reporting on hospital admission, self-control of blood glucose, macrovascular complications, glycaemic control and hypoglycaemic events*

Variable	N	Variable	n
Number of hospital admissions in last year		Self-control of blood glucose (times/day)	
Diabetes related			
0	22	1-5	14
1	3	5-10	14
2-4	3	>10	1
≥5	2	Not recorded	1
Non-diabetes related		Macrovascular complications	
0	20	Yes	7
1	5	No	20
2-4	4	Do not know	2
≥5	1	Not recorded	1
Day time hypoglycaemic events (n/4 weeks)		Night time hypoglycaemic events (n/4 weeks)	
0	5	0	16
1-5	9	1-5	10
5-10	10	5-10	1
≥10	5	≥10	1
Not recorded	1	Not recorded	2
Perceived better glycaemic control with CIPII		Perceived less hypoglycaemic events with CIPII	
Yes	26	Yes	20
No	1	No	1
No difference	2	No difference	8
Not recorded	1	Not recorded	1

One or more macrovascular complications (myocardial infarction, angina, coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), stroke or intermittent claudication) were reported by 23% (n=7); 47% (n=14) reported having hypertension.

Health status and patient satisfaction

Due to missing answers, the SF-12 scores of two out of 30 patients could not be calculated. SF-12 PCS was 37.4 (SD 12.1) and SF-12 MCS was 47.2 (SD 11.1). Mean score on the WHO-5 was 52.7 (SD 28.6) (n=30). Median score for treatment satisfaction was 32 (P^{25}-P^{75}: 28-36; n=28). There where no differences between men and woman regarding scores on SF-12, WHO-5 or DTSQ (p>0.1).

DISCUSSION

With this present study we report details regarding a population of Dutch patients with diabetes mellitus treated with CIPII and cared for in a single centre in the Netherlands. Data were assessed regarding glycaemic control, health status, well-being and treatment satisfaction.

Most available research on CIPII was conducted in either France or the US. Up till now no prospective randomised trials with CIPII have been performed in the Netherlands.

Our results concerning glycaemic control and quality of life are consistent with the results presented by De Vries *et al*. in 2002, who studied part of the population presented in this article. Twenty of 33 patients in their analysis were treated in our hospital at that time.[18] Our report provides further evidence on the long-term efficacy of CIPII regarding glycaemic control and hospital admissions with a mean follow up of 6.0 years. In addition to De Vries *et al.* we now report on treatment satisfaction and well-being.

Our results regarding current health status of patients with diabetes mellitus treated with CIPII are comparable with the health status of patients with diabetes mellitus and comorbidity as reported by Rijken *et al.*[28] Compared with the general Dutch population as reported by Gandek *et al.* the SF-12 MCS of our population is lower.[22]

The mean score on the WHO-5 in our population is much lower than the mean score of around 70 in the general population.[23] The cut-off point for further testing for depression is a score below 50 (raw score below 13). When applying this cut-off point to our data, 39% of our population have an indication for further testing (n=13). The percentage of patients scoring below the cut-off point on the WHO-5 is higher in our population then the percentages reported by Rakovac *et al*. for patients with type 1 and type 2 diabetes, 23 and 30.9% respectively.[29] However, due to the small population size in our study, this difference may be based solely on a sampling error.

The high level of satisfaction with treatment in our study is comparable with the treatment satisfaction levels reported for CSII and MDI by Hoogma *et al.*[27] Home *et al*. reported baseline treatment satisfaction levels of patients with type 1 diabetes mellitus in their randomised controlled trial comparing insulin aspart with human insulin that are also similar to our levels.[30] Although ceiling effects of the questionnaire used have been raised as a point of concern,[31] this will pose less of a problem in a cross-

sectional measurement.[32] To assess future satisfaction, use of the 'Change version' of the questionnaire might be appropriate.[32]

Based on these data we conclude that although treatment satisfaction with CIPII is high and very similar to treatment satisfaction of type 1 diabetes mellitus patients on MDI or CSII, mental health status and well-being of this population are lower than for other treatment modalities. We can only hypothesise about the determinants of these low scores. There is some evidence for the association of duration of diabetes and being female with decreased quality of life, which may partly explain the results found in our study.[33] Mean duration of diabetes at the time of the study was almost 25 years and the percentage of females almost 80%. We do not have the full data on the nature and occurrence of physical symptoms and microvascular complications in our population; these complications will have a negative impact on well-being and health status.[34] Furthermore, we do not know the coping behaviours and personality characteristics of our patients, parameters known to influence quality of life.[35]

Study limitations

The retrospective design is the main limitation of our study. Data on hospital admissions and macrovascular disease were based on self-reporting and this could potentially be a study limitation. Furthermore, we do not have baseline scores for health status, well-being and treatment satisfaction.

CONCLUSION

In conclusion, based on our data, CIPII does improve glycaemic control without increasing the risk of hypoglycaemic events. Furthermore, treatment satisfaction with CIPII is high and in the same range as treatment satisfaction with other intensive treatment modalities. Mental health status and well-being of the patients studied were low, with further investigation regarding depression probably being appropriate in one out of three patients.

To date, CIPII is still a last-resort treatment in the Netherlands. Most patients are concentrated in one clinic. The consequence is that eligible patients sometimes have to travel great distances for evaluation, implantation, refilling and emergencies concerning CIPII. Data on the performance of CIPII in France suggest that CIPII would be an effective treatment option for more patients with diabetes mellitus. Almost all the evidence we have on CIPII comes from French or American studies on the subject. We think there is a need for evidence from other countries where this treatment modality is used.

At this moment, a randomised cross-over clinical trial is being conducted in our centre to provide information about the safety and efficacy of CIPII in patients with diabetes mellitus type 1 and poor glycaemic control. Results of that study will help to answer the question whether CIPII is a safe and effective treatment option for diabetes mellitus.

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