CHAPTER 2

Complications of continuous intraperitoneal insulin infusion with an implantable pump in type 1 diabetes

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Abstract

INTRODUCTION

Continuous intraperitoneal insulin infusion (CIPII) with an implantable pump is a last-resort treatment option for patients with type 1 diabetes (T1DM). In order to monitor the course and to gain more detailed insight in the complications, we performed a follow-up study.

PATIENTS AND METHODS

A retrospective, longitudinal observational cohort study in patients with T1DM that started CIPII between January 1st 2000 and June 1st 2011 was performed. Outcomes were defined as operation free period (OFP), rate and type of complications. Comparisons were made between patients starting CIPII from 2000 and 2007 and from 2007 onwards.

RESULTS

In 56 patients, 70 complications occurred during 283 patient years. Catheter occlusion (33%), pump dysfunction (17%), pain at the pump site (16%) and infections (10%) were the most frequent complications. This resulted in a median OFP of 4.5 years (95% confidence interval 4.1, 4.8) without a difference between the time periods. Fifty re-operations were performed due to complications, one per 5.6 patient years, with a decrease in pump dysfunction (from 4.9 to 1.8 events per 100 patient years, p=0.04) and pump explantations (from 6.6 to 3.5 events per 100 patient years, p=0.02) after 2007. In total, there were 69 hospital re-admissions, with a median duration of 6 days. No CIPII related mortality was reported.

CONCLUSIONS

A significant decrease in pump dysfunction and explantation was seen after 2007 compared to the period 2000-2007. The OFP during the last decade is stable. No CIPII related mortality was reported. CIPII remains a safe treatment modality for specific patient groups

Introduction

Continuous intraperitoneal insulin infusion (CIPII) with an implantable pump is a treatment option for patients with diabetes since the 1980s. Nowadays this treatment modality is mainly used in patients with so called 'brittle diabetes', i.e. failure to reach adequate glycaemic control despite intensive insulin therapy with multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) and/or having frequent hypoglycaemic episodes, or subcutaneous insulin resistance [1,2].

Although the long-term feasibility and positive metabolic benefits of CIPII are established by several clinical studies, reports on the drawbacks of CIPII are relatively scarce [3,4]. Obviously, complications interfere with treatment outcome with respect to glycaemic control, costs and, most importantly, quality of life [5,6]. Furthermore, technical problems prevented widespread use of CIPII in the past, but modifications of both the catheter attached to the pump and the insulin have reduced the incidence of insulin aggregates blocking the insulin delivery; one of the major problems some years ago [7].

Haveman *et al*. underlined this development by studying the complications of CIPII in patients that started with CIPII before 2007 in our hospital (Isala, Zwolle, the Netherlands) [8]. After introduction of a new battery and a change in insulin solution in 2000, the operation free period (OFP) was estimated to increase from 21 to 78 months. The incidence of complications such as pump site infections and catheter related problems decreased, which is in accordance with other studies on CIPII [5,6]. However, ongoing monitoring is necessary to observe the course of this decrease. Moreover, to gather accurate results on what the OFP really is after the changes in 2000, as only limited number of patients at the time of the previous evaluation (follow-up until 2007) had reached a 78 month follow-up. Thus it is essential to extend our former study including the period from 2007 onwards.

Aim of the current study is to describe the complications of CIPII in patients with type 1 diabetes mellitus (T1DM) in the period from 2000 until 2011 in which we will also study in more detail the origin and consequences of both pump- and/or catheter related problems and complications.

Patients and methods

PATIENTS

In the Netherlands, the following indications for CIPII have been formulated: subcutaneous insulin resistance, brittle diabetes, hypoglycaemia unawareness, delayed insulin absorption, allergies, lipohypertrophy and/or lipoatrophy, very lean subjects, needle phobia, severe skin scarring or chronic dermatological problems [9]. Patients were selected for CIPII after consultation with diabetes professionals well acquainted with CIPII, with as a minimum the participation of an internist and a diabetes specialist nurse in the decision making. Implantation was always combined with intensive education and, on indication, assessment by a psychologist.

All patients with T1DM who were treated with CIPII in the period of January 1st 2000 until June 1st 2011 were included in the current analysis. All of these patients were referred to and treated in the Isala. For all patients, detailed clinical data regarding surgical placement of the pump, short- and long-term complications and consequences were collected retrospectively by reviewing hospital charts, operation- and microbiology reports. Data were collected by use of standardized case record forms.

PROCEDURES

Insulin pump, implantation and post-operative treatment and refill procedures have been described previously [8]. In brief, MiniMed MIP model 2007 CIPII devices (Medtronic-MiniMed, Northridge, CA, USA) were implanted in our clinic from 2000 onwards. This model has a reservoir which can contain 15 ml of special solution of U400 insulin and has a battery with 7 years longevity.

An outpatient rinse procedure with NaOH was performed every 9 months or in case of insulin underdelivery. Insulin underdelivery is present when after the pump reservoir is totally emptied, the ratio between programmed and actually infused insulin volume upon programmed insulin, denominated as % error, was calculated. If the % error was higher than 20, or a clinically significant difference between the % error calculated at previous refill was found, a rinse procedure would be performed. In addition, inspection of the patient-pump-communicator for hardware or electronic failure was performed. If these procedures failed to restore normal insulin infusion a catheter flushing and/or catheter x-ray investigation was also performed. In case of signs of intractable occlusion, despite all of these actions, surgical examination of the catheter to discover possible blockages with a post-surgical rinse of the pump was deemed necessary.

COMPLICATIONS

Pump site infection was defined as a culture proven infection in the subcutaneous pocket of the insulin pump. Prolonged device related pain was defined as pain at the pump site which lasted for more than 6 weeks after surgery and necessitated use of analgesics. Cutaneous erosion of the skin was defined as redness with signs of (imminent) perforation of the overlying skin at the pump site. Post-operative haematoma was defined as a swelling at the pump site caused by bleeding. Pump dislocation was defined as migration or rotation of the pump relative to the initial place of implantation. Catheter occlusion was defined as blockage of the catheter by fibrin clots or an intrinsic catheter defect. Encapsulation in the peritoneal cavity was defined as encapsulation of the catheter tip, which is positioned in the peritoneal cavity, by the omentum as diagnosed by catheter x-ray investigation or during surgical inspection. Hardware problems were defined as demonstrated hardware failure of the pump. Premature battery end of life was defined as battery end of life within 3.5 years of implantation. Pump dysfunction was defined as acute or chronic dysfunction of the pump after excluding of other causes e.g. battery end of life or hardware failure.

STATISTICAL ANALYSIS

All statistical analysis were performed with SPSS software (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Descriptive statistics include number (percentage), mean (standard deviation (SD)) and median (interquartile range [IQR]). Data were compared with the Fisher's exact test in case of categorical data. In case of continuous data, Student's t-test or Mann-Whitney U test were used if the data was distributed normally or skewed, respectively. Q-Q plots and histograms were used to determine if the tested variable had a normal distribution or not. The OFP was calculated as the time from initial implantation to the date of first documented re-operation. If patients had not experienced an operation, they were censored at the date of last follow-up or time of death. Kaplan-Meier curves were constructed to visualize the OFP. In order to further analyse the course of the complications, subanalyses were made between patients starting CIPII from 2000 and 2007, the end of the previous study, and from 2007 onwards. Differences in time until occurrence of complications and the OFP rates were assessed for statistical significance using the log-rank test. A Cox regression analysis was performed to study the influence of possible confounders (age, sex, body mass index (BMI)), duration of diabetes) on the OFP. A (two-sided) p-value of less than 0.05 was considered statistically significant.

Results

PATIENTS AND IMPLANTATION PROCEDURES

A total of 57 patients with T1DM were treated with CIPII. One patient with self-induced complications was excluded from analysis; the remaining 56 patients are subject of this study. Patient characteristics are depicted in Table 1. Two hundred eighty-three patient years of follow-up were observed, with a median duration of 4.7 [3.7, 7.3] years. In total, 80 pumps were implanted; 20 (35.7%) patients had a second pump and 4 (7.1%) patients had a third pump implanted.

TABLE 1 Baseline characteristics of patients starting CIPII.

	All patients 2000 - 2011 (n=56)	**Implantation period** 2000 - 2007 (n=37)	2007 - 2011 (n=19)
Age (years)	37.6 (14.5)	38.0 (14.4)	36.6 (15.1)
Female sex (n)	38 (68)	28 (76)	10 (53)
Smokers (n)	12 (21)	7 (19)	5 (26)
Previous abdominal operation (n)	9 (16)	7 (19)	2 (11)
BMI (kg/m^2)	25.4 (4.4)	26.3 (4.2)	23.7 (4.3)
Duration of diabetes (years)	16.7 [9.7, 26.3]	15.9 [9.8, 26.8]	19.1 [9.6, 26.3]
Retinopathy (n)	13 (23)	9 (24)	4 (21)
Neuropathy (n)	17 (30)	12 (32)	5 (26)
Nephropathy (n)	4 (7)	3 (8)	1 (5)

Data are presented as n (%), mean (SD) or median [IQR]. Abbreviations: BMI, body mass index; CIPII, continuous intraperitoneal insulin infusion.

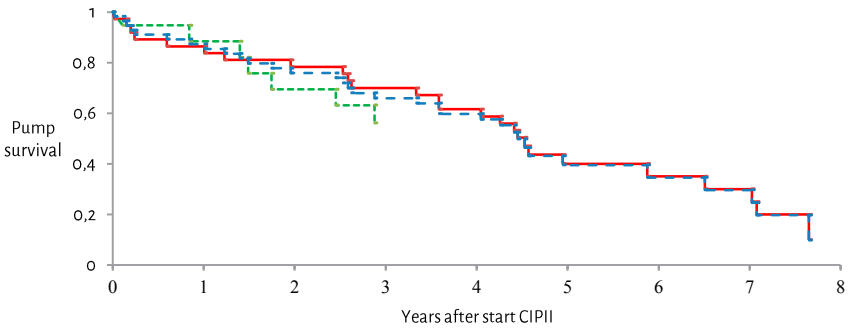
OPERATION FREE PERIOD

After starting CIPII, 33 patients underwent re-operation; 6 due to expected battery end of life, 24 due to complications and 3 due to other reasons. As presented in Figure 1, the median OFP between initial implantation and the first re-operation for all patients was 4.5 years (95% confidence interval (CI) 4.1, 4.8). After excluding operations for pump replacement for expected battery end of life or other reasons (n=9) the median OFP was 4.5 years (95% CI 3.9, 5.0).

COMPLICATIONS

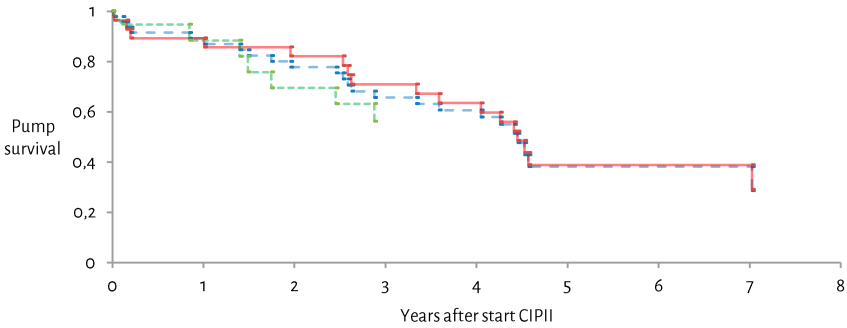
A total of 70 complications occurred during the follow-up; see Table 2. Catheter occlusion (32.9%), pump dysfunction (17.1%) and pain at the pump site (15.7%) were the most frequent

FIGURE 1 Time between initial implantation and first re-operation, for all reasons.



The dotted blue line represents all patients. The red line and green line represents the patients who started CIPII between 2000 and 2007 and between 2007 and 2011, respectively (log-rank test for differences p=0.80). Abbreviations: CIPII, continuous intraperitoneal insulin infusion.

FIGURE 2 Time between initial implantation and first re-operation, only for complications.



The dotted blue line represents all patients. The red line and green line represents the patients who started CIPII between 2000 and 2007 and between 2007 and 2011, respectively (log-rank test for differences p=0.72). Abbreviations: CIPII, continuous intraperitoneal insulin infusion.

complications. Fifty-seven complications occurred with the first implanted pump in situ, 11 with the second and 2 with the third. Twenty-one patients did not experience any complication, 15 patients experienced 1 complication, 11 patients 2 complications, 7 patients 3, 1 patient 4 and 1 patient 8 complications. The latter patient had recurrent infections and peritonitis, after a catheter replacement procedure. The median time from implantation of the first pump until occurrence of the first complication (excluding battery end of life) was 3.6 years (95% CI 2.2, 5.0).

TABLE 2 Complications of CIPII during follow-up.

	All patients 2000 - 2011 (n=56)			Implantation period 2000 - 2007 (n=37)			2007 - 2011 (n=19)		
	n	%	Per 100 PY	n	%	Per 100 PY	n	%	Per 100 PY
Haematoma	3	4.3	1.1	2	3.8	0.9	1	5.9	1.8
Infection	7	10.0	2.5	4	7.5	1.8	3	17.6	5.3
Pain	11	15.7	3.9	8	15.1	3.5	3	17.6	5.3
Cutaneous erosion	2	2.9	0.7	2	3.8	0.9	0	0.0	0.0
Dislocation	3	4.3	1.1	2	3.8	0.9	1	5.9	1.8
Hardware failure	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0
Premature battery end of life	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0
Insulin aggregate	4	5.7	1.4	4	7.5	1.8	0	0.0	0.0
Catheter occlusion	23	32.9	8.1	16	30.2	7.1	7	41.2	12.3
Encapsulation of the catheter tip	3	4.3	1.1	3	5.7	1.3	0	0.0	0.0
Peritonitis	1	1.4	0.4	1	1.9	0.4	0	0.0	0.0
Pump dysfunction	12	17.1	4.2	11*	20.8	4.9	1*	5.9	1.8
Other	1	1.4	0.4	0	0.0	0.0	1	5.9	1.8
All	70	100.0	24.8	53	100.0	23.5	17	100.0	29.9

Abbreviations: BMI, body mass index; CIPII, continuous intraperitoneal insulin infusion; PY, patient years.* p=0.04.

TABLE 3 Re-operations due to complications of CIPII during follow-up.

	All patients 2000 - 2011 (n=56)			Implantation date 2000 - 2007 (n=37)			2007 - 2011 (n=19)		
	n	%	Per 100 PY	n	%	Per 100 PY	n	%	Per 100 PY
Catheter inspection	2	4.0	0.7	2	5.3	0.9	0	0.0	0.0
Catheter replacement	13	26.0	4.6	8	21.1	3.5	5	41.7	8.8
Explantation of pump and catheter	17	34.0	6.0	15*	39.5	6.6	2*	16.7	3.5
Repositioning of pump	2	4.0	0.7	2	5.3	0.9	0	0.0	0.0
Fixation of pump	2	4.0	0.7	1	2.6	0.4	1	8.3	1.8
Cutaneous problem	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0
Intra-abdominal problem	1	2.0	0.4	1	2.6	0.4	0	0.0	0.0
Remove clot at tip of catheter/ Flush catheter	7	14.0	2.5	4	10.5	1.8	3	25.0	5.3
Haematoma	1	2.0	0.4	1	2.6	0.4	0	0.0	0.0
Reposition of catheter	3	6.0	1.1	3	7.9	1.3	0	0.0	0.0
Infection	2	4.0	0.7	1	2.6	1.2	1	8.3	1.8
All	50	100.0	17.7	38	100.0	44.3	12	100.0	21.1

Abbreviations: BMI, body mass index; CIPII, continuous intraperitoneal insulin infusion; PY, patient years.* p=0.02.

CONSEQUENCES OF COMPLICATIONS

Due to complications, 50 re-operations were performed, one per 5.6 year of follow-up; see Table 3. Explantation of the pump and catheter (34.0%, 6.0 per 100 patient years) and catheter replacement (26.0%, 4.6 per 100 patient years) were the most frequently performed

re-operations. Nine episodes of ketoacidosis occurred during follow-up, in 8 due to pump dysfunction and 1 due to catheter occlusion. Sixty-nine episodes of hospital re-admissions were caused by complications. The median duration of re-admission was 6 [3.0, 12.8] days.

COURSE OF COMPLICATIONS

Between 2000 and 2007, 37 (median follow-up 5.3 [4.7, 6.7] years) patients received a pump and 19 (median follow-up 3.7 [1.4, 4.3] years) patients received a pump between 2007 and 2011. The clinical characteristics of patients in the two different timeframes were comparable and also showed no differences in median OFP (log-rank: p=0.80), even when excluding operations for expected battery end of life and other reasons than complications (log-rank: p= 0.72); see Figures 1 and 2. The number of pump dysfunctions among patients who started CIPII after 2007 was significant lower compared to the group of patients who started CIPII before 2007 (p=0.04); see Table 2. As shown in Table 3, from 2007 onwards there were significant less re-operations for pump and catheter explantation due to complications (p=0.02). The Cox regression analysis showed a non-significant hazard ratio of 1.12 (95% CI 0.46, 2.75, p=0.52) for patients implanted after 2007 compared to those who were implanted between 2000 and 2007. None of the confounders had a significant relation with time to first re-intervention.

MORTALITY AND CESSATION OF CIPII THERAPY

During the follow-up period, one patient died due to heart failure whilst treated with CIPII. In 5 patients, CIPII was stopped and the pump removed. In two patients the pump was removed because of recurrent infections. In the other cases because of pain (n=1), inadequate glycaemic control (n=1) or at own choice (n=1). The remaining 50 patients are still treated with CIPII.

Discussion

The current study describes the incidence of complications in 56 T1DM patients treated with CIPII with an implanted insulin pump during the last decade. During 283 patient years of follow-up, 70 complications occurred, i.e. one complication per 4.0 patient years. Catheter occlusion (32.9%), pump dysfunction (17.1%), pain (15.7%) and infections (10.0%) were the most frequent complications. A significant decrease in pump dysfunction and the need of premature explantation of the pump was seen since 2007 as compared to before 2007. There was a non-significant but potentially relevant increase in infections, catheter related complications and re-operations since 2007, which did not affect the OFP during the last decade, however.

The incidence of infections in the present study, 2.5 per 100 patient years, is comparable to previous studies on CIPII and other implanted devices [5,6,8,10–13]. Apparently, this rate has increased in patients operated after 2007 to a number of 5.3 infections per 100 patient years. However, all infections appeared in one patient. Due to combined improvements in pump technology, insulin stability and frequent rinse procedures the high incidence of catheter blockage (between 7.8 and 57.3 per 100 patient years) in the past has been substantially reduced [4,14–19]. In 2003, Gin *et al*. reported an incidence of 3.7 catheter obstructions with need of surgical intervention, per 100 patient years [6]. Though we found no difference in the course, compared to the scarce recent literature on this topic, the incidence of catheter occlusions and re-operation for catheter replacement (12.3 respectively 8.8 per 100 patient years) since 2007 are rather high compared to the findings of Gin *et al*.

Besides the number of re-operations, the impact of complications are illustrated by the number of ketoacidosis occurrences (n=9) and the hospital re-admissions (n=69 with a median duration of 6 days) due to complications. DeVries *et al*. showed that initiation of CIPII diminishes the median duration hospital stay for patients with poorly regulated diabetes from 45 days in the year before implantation to 13 days in the year after implantation, the latter mostly due to implantation of the pump [1]. As far as we know, the present study is the first to report on the number of hospital re-admissions due to complications. This number is needed to strengthen future analysis of cost-effectiveness and quality of life of CIPII.

This study has limitations. First, since the follow-up of the study performed by Haveman *et al*. ended at January 1st 2007 we decided to use this point in time as cut-off for our subanalyses for the course of the complications in time [8]. Although this date is arbitrary and the numbers of patients are small, it can aid to get insight in changes of complications, positively and negatively, specific for a timeframe, that would need attention for present care of these patients. Second, the exact cause of catheter or pump dysfunction could not always be retrieved; therefore the rate of e.g. insulin aggregates that have led to pump dysfunction may be underestimated.

Conclusion

The median OFP for patients treated by CIPII with an implantable pump has been stable over the last decade: 4.5 years. Catheter occlusion (32.9%), pump dysfunction (17.1%), pain at the pump site (15.7%) and infections (10.0%) were the most frequent complications. There was

a significant decrease in the number of pump dysfunctions and pump explantations and no significant alterations in the course of complications between the period from 2000 until 2007 and from 2007 onwards. However, the former group had a longer follow-up period. This may mask a transition or possible future increase of complications and re-operations, thus yielding a relative stable OFP among patients. It will require ongoing investigation and thorough monitoring during the upcoming years.

In addition, since a new intraperitoneal insulin formulation had to be introduced in 2011 since there are no batches of the original insulin formulation left, the findings of the present study should be taken into account when evaluating the effects associated with the use of the new insulin formulation. No CIPII related mortality was reported. CIPII remains a safe treatment modality for specific patient groups.

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PART II

Effects of intraperitoneal insulin therapy - glycaemia, quality of life and treatment satisfaction

CHAPTER 3	Glycaemic control, quality of life and treatment satisfaction after 6 years intraperitoneal insulin infusion with an implantable pump
CHAPTER 4	A long-term comparison between continuous intraperitoneal insulin infusion and subcutaneous insulin therapy among patients with poorly controlled T1DM: a 7 year case-control study
CHAPTER 5	Intraperitoneal insulin infusion is non-inferior to subcutaneous insulin infusion in the treatment of type 1 diabetes: a prospective matched-control study
CHAPTER 6	Quality of life and treatment satisfaction among type 1 diabetes mellitus patients treated with continuous intraperitoneal insulin infusion or subcutaneous insulin: a prospective observational study
CHAPTER 7	Continuous intraperitoneal insulin infusion versus subcutaneous insulin therapy in the treatment of type 1 diabetes: positive effects on glycaemic variability