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ORIGINAL ARTICLE

Surgical aspects and complications of continuous intraperitoneal insulin infusion with an implantable pump

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Abstract
Purpose Continuous intraperitoneal insulin infusion (CIPII) with an implantable pump is safe and effective in selected subjects with diabetes. Our aim was to assess surgical experience and complications with CIPII.
Methods We performed a retrospective longitudinal observational cohort study of patients that started with CIPII from 1990 to 2006. Operation free period and complication rate were compared between patients initiating CIPII before 2000 and from 2000 onwards.
Results In 63 patients, 166 re-operations were performed during 381 patient-years. Re-operations were pump replacement due to end-of-battery life (47%), laparoscopic catheter-related procedures (29%) and other interventions (24%). Median operation free period increased from 21 to 78 months from 2000 onwards ($p=0.039$). Nineteen percent of patients developed complications. No operation-related mortality was reported.
Conclusions Increased experience together with technical improvements has led to an increase of the operation free period. The absence of procedure-related mortality and a low complication rate makes CIPII feasible for selected patients with diabetes.

Keywords Insulin infusion systems · Diabetes mellitus · Surgery · Complications

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Introduction

Continuous intraperitoneal insulin infusion (CIPII) with an implantable insulin pump has been available as a treatment option in patients with diabetes mellitus for more than 25 years already. Its safety and efficacy has been reported by the Evaluation of Active Implants in Diabetes (EVADIAC) study group and others [1–6]. Better glycaemic control in terms of lower HbA_{1c}, decreased number of hypoglycaemic events and reduced glycaemic variability can be achieved and patients' treatment satisfaction is high [1–8]. This therapy mode is only available in a limited number of countries where CIPII is mainly used in patients who, despite intensive (continuous) subcutaneous insulin therapy, do not reach acceptable glycaemic control and/or have frequent hypoglycaemic episodes (especially when accompanied by

hypoglycaemia unawareness) and/or have subcutaneous insulin resistance.

Studies focusing on the surgical aspects of CIPII are relatively scarce. Udelsman et al. reported regarding 21 patients started on CIPII between 1986 and 1991 in an American centre needing one surgical re-intervention per 1.7 patient-years without occurrence of mortality [9]. This group published an update in 2000 reporting the same rate of re-interventions in 28 subjects [10]. At the time of these reports, the pump battery lasted approximately 2.5 years and many re-interventions were needed because of the necessity of pump replacement after battery depletion [9]. One re-intervention per 10.9 patient-years was related to catheter problems [9]. Three times a pump was explanted because of pump-site infections during a total of 153 patient-years (1 in 51 patient-years) [9]. Others reported incidences of pump-site infection of 1 per 53 and 56 patient-years and of re-intervention because of catheter problems or electronic failure of 1 per 22 patient-years, respectively [11, 12].

All above discussed reports contain only patients included before 2000. However, since then, many innovations have been made. Battery life is increased to a maximum of 7 years and the insulin solution used nowadays results in reduced incidence of insulin aggregate formation and thereby less catheter obstructions [13]. The purpose of this study is to describe the surgical implications and complications in a large group of patients treated with CIPII in The Netherlands. Furthermore, we studied whether increased experience with the procedure and improvements to the pump in 2000 led to a decreased necessity for re-intervention surgery.

Materials and methods

Patients

Patients were selected for CIPII after consultation with the diabetes team consisting of an internist and a diabetes specialist nurse. Indications for CIPII in The Netherlands are 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 (especially when accompanied by hypoglycaemia unawareness) and/or having subcutaneous insulin resistance. Other indications for CIPII are allergy to needles and/or tape making MDI and CSII impossible, absence of subcutaneous fat, making CSII not feasible. Implantation was always combined with intensive education and on indication with assessment by a psychologist.

All patients who received their first implantable insulin pump for CIPII between 1990 through 2006 were included in the study and retrospectively analysed. All patients on CIPII in The Netherlands are implanted in one hospital, Isala clinics, Zwolle. Glycaemic control, health status and treatment satisfaction of this patient group have been described previously [7]. Patient data were retrieved from clinical and surgical reports.

Insulin pump

In our clinic, the MiniMed MIP 2001 (Medtronic-MiniMed, Northridge, CA, USA) was implanted since the 1980s. This model had a lithium cell battery with a battery life of approximately 2.5 years. From 2000 onwards, the MIP model 2007, with a battery life of approximately 7 years, is used for all implantations and replacements. Both models have a reservoir to contain up to 15 ml U400 insulin which is maintained at negative atmospheric pressure. The pump has a diameter of 8 cm and is 2 cm thick. The 2007 model is slightly lighter (131 g, without insulin) than the previous model (145 g).

A silicone catheter is attached to the side port of the pump, through which the insulin is delivered directly into the peritoneal cavity. Insulin delivery is remotely controlled by the patient with a pager-sized personal pump communicator.

Implantation and post-operative treatment

Before pump implantation, the endocrinology team filled and primed the pump on a sterile table in the operating theatre. This means that when the pump is handed to the surgeons, it is immediately functional.

After induction of general anaesthesia, a first generation cephalosporin is administered intravenously. The abdominal skin is carefully cleaned with chlorhexidin and a sterile plastic is draped on the skin. A transverse incision is made in an abdominal quadrant, selected pre-operatively by the patient and the diabetes specialist nurse. After dissection of the subcutaneous tissue, a subcutaneous pocket is created. Thereafter, to create an entrance to the intraperitoneal cavity for the catheter, the anterior fascia of the rectus abdominis is incised, the fibres of the rectus muscles are spread and the posterior rectus sheath is opened. The peritoneum is opened and the tip of the catheter is carefully inserted and directed to the right upper quadrant or the Douglas pouch of the peritoneal cavity. A purse-string suture is placed on the peritoneum and the flange is sutured just behind the anterior rectus fascia. The pump is sutured into the subcutaneous pocket after placing a gentamicin gauze (Fig. 1). The wound is closed in layers.

Post-operatively, to minimise pain and the development of pump-pocket seroma, 24 h strict bed rest is maintained and a supportive belt is prescribed for 4–6 weeks. Furthermore, patients are instructed not to lift heavy weights and not to engage in strenuous physical exercise during the first 6 weeks after surgery. In general, patients are discharged from the hospital on the third or fourth post-operative day, depending on the ability and confidence of the patient to use the implantable pump.

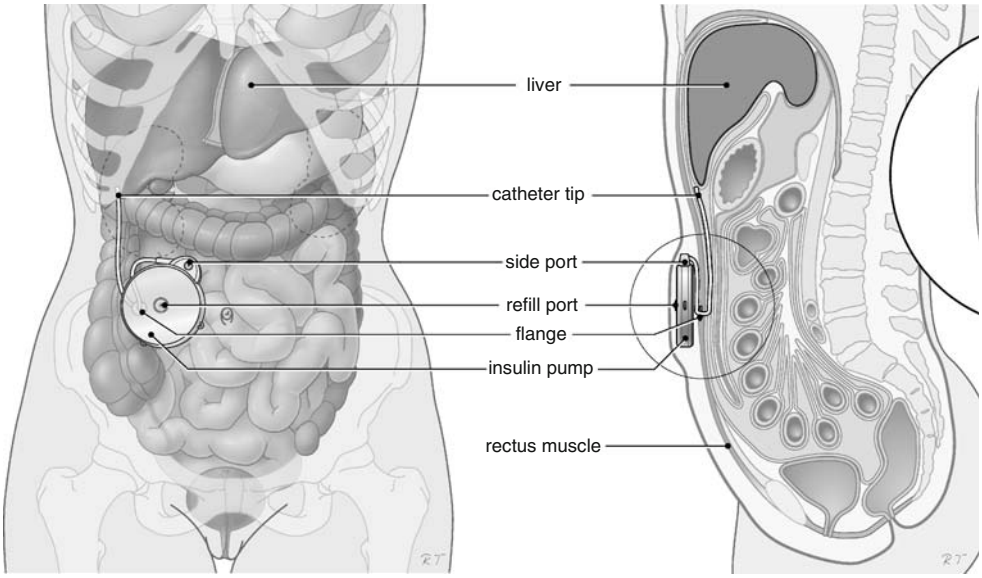


Fig. 1 Insulin pump and catheter in vivo. Schematic representation of the position of the insulin pump and catheter in vivo

Refill and rinse procedures

The pump insulin reservoir is refilled at the outpatient clinic transcutaneously at least every 3 months, depending on the individual's insulin requirement. Obstruction by insulin aggregation in the pump or catheter can be treated with rinse procedures. Buffer and/or NaOH alkaline solution (0.1 M) is flushed through the pump or separately through the catheter, using the side port. Performing these procedures on a regular basis can partly prevent total blockage of the system by removing the partial stenosis caused by insulin precipitation. Since recently changing protocols, rinse procedures are carried out every 9 months or when marked under delivery of insulin is noted either by the patient or during refill procedures.

Complications

Pump-site infection was defined as a culture proven infection in the subcutaneous pocket of the insulin pump. Prolonged pain was defined as pain of the pump site which lasted for more than 6 weeks after surgery. 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 re-bleeding. Small post-operative seromas were not classified as a complication as it always had a mild presentation which resolved completely in all cases without re-intervention.

Statistical analysis

Descriptive statistics include number (percentage), mean (standard deviation, SD) and median (interquartile range). Patient characteristics were compared with the chi-square test in case of categorical data, and in case of continuous data, Student's t tests (normal distribution) or Mann–Whitney U test in case of skewed data. Q–Q plots were performed to determine whether the data had a normal distribution. For comparison of the operation free period, the log-rank test was used with construction of Kaplan–Meier curves for visualisation. A Cox regression analysis was performed to study the influence of possible confounders (age, sex, body mass index (BMI), duration of diabetes, the presence of retinopathy, neuropathy and nephropathy). A p value of less than 0.05 was considered statistically significant.

Results

Patients and procedures

Between 1990 through 2006, 63 patients were treated with CIPII and all are included in our analyses. Patient characteristics are shown in Table 1. Mean age at first pump implantation was 38 (14) years, 47 (75%) patients were female and most had type 1 diabetes mellitus (58 patients; 92%). Notably, more microvascular complications were present in patients with an implantation before 2000.

In 381 patient-years, one re-intervention per 2.3 patient-years was performed. A new insulin pump was implanted in 78 (47%) cases, due to expected end-of-battery life. In 32 (19%) cases, laparoscopy was performed during which a fibrin plug could be removed from the catheter tip to resolve pump dysfunction. In 17 (10%) cases, the whole catheter was replaced to resolve pump dysfunction due to obstruction by insulin crystals. Pump removal was performed in 21 (13%) cases for several reasons. Other operations were performed 18 (11%) times, including

Table 1 Patient characteristics at start of CIPII

	Implantation date	
	Before 2000 (n=28)	In and after 2000 (n=35)
Age (years)[a]	38 (12)	37 (15)
Female sex	19 (68)	28 (80)
Type 1 diabetes	23 (82)	34 (97)
Duration of diabetes (years)[b]	17 (12–21)	15 (9–26)
BMI (kg/m^2)[a]	25.0 (4.8)	26.2 (4.7)
Nephropathy	5 (18)	2 (6)
Neuropathy	16 (57)	7 (20)**
Retinopathy	15 (54)	10 (29)*

Values are number of patients (percentages) unless indicated otherwise
CIPII continuous intraperitoneal insulin infusion
*p=<0.05; **p=<0.01
[a] Mean (SD)
[b] Median (interquartile range)

moving the pump to another side because of infection or pain and removal of haematoma (see Table 2).

Operation free period

In order to investigate whether the operation free period increased with our increasing experience with pump implantation and increased battery durance, we divided our population in two groups, i.e. patients implanted before 2000 (n=28) and in or after 2000 (n=35). Patients underwent a median number of 2 (1–6) operations. We calculated the median operation free period between the first and second operation. This operation free period increased from 21 (95% confidence interval (CI) 10–33) months for patients operated initially before 2000 to 78 (95% CI 13–79) months for patients operated in or after 2000 (p=0.039; log-rank test, see Fig. 2). After excluding operations for pump replacement after expected battery end-of-life, this difference remained statistically significant (p=0.048). Of the 35 patients operated after 2000, 21 patients are still without a second operation, ranging from 5 to 77 months after pump implantation.

The Cox regression analysis showed that patients implanted in or after 2000 had a hazard that was nearly halve (hazard ratio (HR)=0.46, 95% CI 0.21–1.00) of that for those who were implanted before 2000. None of the confounders had a significant relation with time to first re-intervention. After excluding operations for pump replacement after expected battery end-of-life, the HR dropped to 0.28 (95% CI 0.09–0.82; p=0.020). See supplementary material.

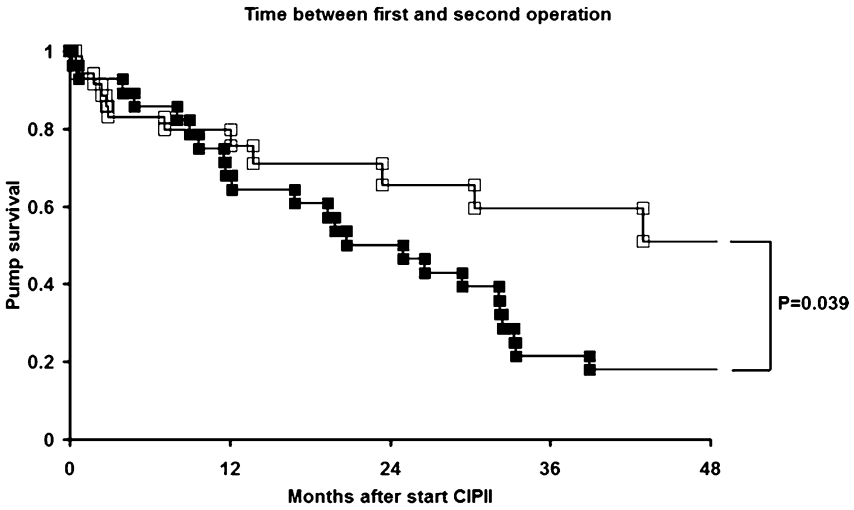
Complications

Twelve patients (19%) developed 19 complications, of which local infection and pain were most common

Table 2 Surgical procedures and complications during follow-up

	Implantation date				All	
	Before 2000		In and after 2000			
	n	%	n	%	n	%
Patients	28		35		63	
Patient-years	294		87		381	
Surgical procedures						
New pump implantation	70	53.4[a]	8	22.9[a]	78	47.0[a]
Laparoscopy	22	16.8[a]	10	28.6[a]	32	19.3[a]
Catheter replacement	16	12.2[a]	1	2.9[a]	17	10.2[a]
Pump removal	14	10.7[a]	7	20.0[a]	21	12.7[a]
Temporarily	6		3			
Definitively	8		4			
Pump relocation	3	2.3[a]	3	8.6[a]	6	3.6[a]
Other	6	4.6[a]	6	17.1[a]	12	7.2[a]
All	131	100.0[a]	35	100.0[a]	166	100.0[a]
Complications						
Pump-site infection	4	44.4[b]	5	50.0[b]	9	47.4[b]
Pain of pump	3	33.3[b]	3	30.0[b]	6	31.6[b]
Cutaneous erosion	2	22.2[b]	1	10.0[b]	3	15.8[b]
Post-operative haematoma	–	–	1	10.0[b]	1	5.3[b]
All	9	100.0[b]	10	100.0[b]	19	100.0[b]

[a] Percentage of surgical procedure within implantation date group
[b] Percentage of complication within implantation date group



Operated before 2000					
Patients at risk	28	19	14	6	4
Events	0	9	14	22	23
Operated after 2000					
Patients at risk	35	19	12	9	4
Events	0	7	10	11	12

Fig. 2 Time between first and second operation in patients on CIPII before compared to in or after 2000. Kaplan–Meier curve from start of CIPII to first consecutive intervention. *Closed squares* indicate patients initially operated before 2000; *open squares* indicate patients initially operated in or after 2000. *CIPII* continuous intraperitoneal insulin infusion

(Table 2). Nine (one in 3.1 patients) complications developed before 2000 and ten (one in 3.5 patients) after 2000. Five patients developed nine pump-site infections in the post-operative period, from 2 weeks till 5 months after implantation. Four infections appeared before 2000 (1 in 73.5 patient-years) and five infections in and after 2000 (1 in 17.4 patient-years), in which period 1 patient had four episodes of infection. In two cases, the pump was removed and re-implanted in a new pocket on the opposite side of the abdomen after complete resolvement of the infection, in one patient with good success. Unfortunately, in the other patient, a recurrent pump-site infection occurred for three more times and this led to the decision to completely discontinue CIPII treatment. In another patient, pump-site infection was also treated with pump removal. Because to date the infection has not settled yet, a new pump is not implanted yet and the patient is on intravenous insulin infusion in the meantime. Pump-site infection was treated in two patients with percutaneous flushing of the pocket with antibiotics, after which CIPII could be continued without further complications in one of these patients; in the other patient, this procedure was not successful, so the pump was removed and re-implanted after complete recovery of the infection. Six patients developed prolonged pain after implantation, which was successfully treated with oral analgesics in two patients. In one and two patients, slight relocation of the pump within its pocket and relocation to a new pocket, respectively, were successful in alleviation of symptoms. Pain was relieved in one patient with laparoscopy, during which several adhesions were cut. In three patients, cutaneous erosion of the overlying skin was seen. In one patient, the pump was moved to another quadrant of the abdomen; two other patients had very little subcutaneous fat, so we moved the pump under the fascia of the rectus abdominis. This led to a satisfactory situation, although refill and rinse procedures were more painful due to this alternative location. Local anaesthesia with lidocaine is therefore used during these procedures. In one patient, a post-operative haematoma was removed from the pocket, after which CIPII was continued without further complications.

Mortality and cessation of CIPII

During the follow-up period, six patients died; none of the deaths were related to post-operative or pump-related complications. Five patients died of diabetes-related complications, due to kidney (n=3) or heart failure (n=2) and one of mesenteric ischaemia whilst treated with CIPII.

In 11 patients, CIPII was stopped and the pump removed. In two patients, the pump was removed because of recurrent infections, as described above. In other cases, CIPII was discontinued because of pump failure (n=3),

inadequate glycaemic control (n=3), kidney–pancreas transplantation (n=2) and psychological reasons (n=1).

Discussion

This study shows that during more than 15 years of experience with CIPII in our centre, the operation free period of these patients increased from 1.8 to 6.5 years and is currently almost at its maximum. Ideally, only one procedure in 7 patient-years is needed to replace the pump when the battery has been depleted. This increase can mainly be attributed to the increased battery durance of the insulin pumps and the standardisation of rinse procedures, preventing the accumulation of insulin aggregates to cause pump malfunction. Our current report shows that despite the requirement of re-intervention surgery during follow-up, CIPII is safe, without pump or operation-related mortality and with a low complication rate. More than 80% of our patients has not experienced any pump-related complications and our pump-site infection rate of 2.4 per 100 patient-years is comparable with that in literature [10, 12, 13]. This infection rate was higher in the patients operated in or after 2000 (1 in 73.5 versus 1 in 17.4 patient-years). However, this is mainly due to one patient operated after 2000 who developed four pocket-site infections. This infection rate compares favourably with that of other implanted devices, like implantable defibrillators or mechanical heart valves with a reported infection rate of 2.5–4.0 per 100 patient-years [14, 15].

The most important drawback of CIPII is the high costs of this kind of treatment. Not only the pump itself, which currently costs approximately 36,000 Euros, but also the special insulin used and the need for regular filling and rinsing procedures performed by diabetes specialist nurses during outpatient sterile procedures make CIPII a very costly treatment option. Whether or not this treatment can be cost-effective compared to the external insulin pump therapy, when long-term diabetes complications, prevented hospital admissions and loss of workdays are taken in to account, remains to be investigated. The only cost analysis with CIPII up to now was done by Haardt et al. more than 15 years ago [16]. Compared to multiple subcutaneous injections, direct costs of CIPII were 2.6-fold higher [16]. Another potential drawback might be the increase in anti-insulin antibodies in CIPII patients compared with CSII patients; however, this does not lead to an increase in clinical or sub-clinical autoimmune disease [17].

As far as we know, this study reports on one of the largest groups of patients treated with CIPII in a single centre with a follow-up exceeding 15 years. Only the French EVADIAC collaborative has a combined experience that exceeds the presented one [13].

Our study has its limitations. Its retrospective design might lead to an underestimation of the complication rate. However, we systematically analysed hospital and operation records of all patients that received CIPII in the studied period in our hospital. Due to the intensive contact patients have with the diabetes team, it is highly unlikely that any cases are missing in the current report. On the other hand, many of the pumps that were implanted after 2000 are still functioning without the need for re-intervention yet, possibly resulting in an overestimation of the reported re-intervention rate in that group.

Conclusion

Increased experience with CIPII in our centre together with technical improvements of the pump has led to an almost fourfold increase of the operation free period. The operation free period is almost at its maximum and is currently mostly limited by pump battery life. The absence of pump or operation-related mortality and the relatively low complication rate make CIPII a feasible treatment alternative for selected patients with diabetes that cannot reach adequate glycaemic control with other intensified insulin regimens.

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