Improved glycemic control with intraperitoneal versus subcutaneous insulin in type 1 diabetes. A randomized controlled trial

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**Objective**-Continuous intraperitoneal insulin infusion (CIPII) with an implantable pump has been available for the past 25 years. CIPII, with its specific pharmacodynamic properties, may be a viable treatment alternative to improve glycemic control in patients with type 1 diabetes for whom other therapies have failed. There have been few studies in which CIPII was compared with subcutaneous (SC) insulin treatment for patients with type 1 diabetes with poor glycemic control.

**Research Design and Methods**-In an open-label, prospective, crossover, randomized, 16-month study, the effects of CIPII and SC insulin were compared in 24 patients. The primary outcome measure was the incidence of hypoglycemia. Secondary outcome measures were glycated hemoglobin (HbA1c), and glucose profile, including time in euglycemia, as measured by continuous glucose monitoring.

**Results**-The incidence of grade 1 hypoglycemic events was 4.0±2.6 per week with SC insulin compared with 3.5±2.3 per week during CIPII (p=0.13). The absolute mean difference in HbA1c with CIPII as compared with SC treatment was -0.76% (95% CI:-1.41,-0.11) (p=0.03). Baseline time spent in euglycemia was 45.2±12.6% and increased 10.9% (95%CI:4.6,17.3) with CIPII compared to SC treatment (absolute value; p=0.003). There were no differences in the occurrence rate for severe hypoglycemic events, daily insulin use, or BMI. No pump or catheter malfunction was observed during the study.

**Conclusions**- Though we did not observe a significant reduction in hypoglycemic events, improved glycemic control was achieved with the use of CIPII. We saw a 0.8% decrease in HbA1c and an 11% increase in the time spent in euglycemia.
META-ANALYSES CONCLUDE THAT CONTINUOUS SUBCUTANEOUS INSULIN INFUSION (CSII) IS SOMewhat better than multiple daily injections (MDI) for obtaining glycemic control in patients with type 1 diabetes (1-4). These differences tend to be smaller when synthetic analogues are used. The absorption of subcutaneous (SC) infused insulin is influenced by many factors, sometimes responsible for unexpected hypo- and hyperglycemic events (5, 6). In some patients with type 1 diabetes, this form of therapy does not yield acceptable and stable long-term glycemic control (7).

The intraperitoneal administration of insulin allows blood glucose values to normalize more rapidly after a meal with more predictable insulin profiles compared to SC insulin (8-10). Much of the intraperitoneal insulin is absorbed through the portal system, which more closely mimics normal physiological action, resulting in improved hepatic uptake and lower peripheral plasma insulin levels (11). This may lead to improved glucagon secretion and hepatic glucose production in response to hypoglycemia (12).

The effects of continuous intraperitoneal insulin infusion (CIPII) in type 1 diabetes have been investigated in few randomized controlled trials, and all were done before the era of rapidly acting insulin analogues. The objective of our study was to assess the safety and efficacy of CIPII compared to intensified SC insulin therapy in patients with inadequately controlled type 1 diabetes.

RESEARCH DESIGN AND METHODS

**Study Population:** Subjects with type 1 diabetes with low fasting c-peptide concentrations (<0.20 nmol/L), with intermediate or poor glycemic control, defined as glycated hemoglobin (HbA1c) ≥7.5% and/or ≥5 incidents of hypoglycemia (<4.0 mmol/L) per week, aged 18 to 70 years, treated with MDI or CSII, were eligible for the study. The exclusion criteria included: impaired renal function (plasma creatinine ≥150 µmol/L or glomerular filtration rate as estimated by the Cockcroft-Gault formula ≤50 ml/min) (13); cardiac problems (unstable angina or myocardial infarction within the previous 12 months or New York Heart Association class III or IV congestive heart failure); insulin allergy; mentally handicapped, current or past psychiatric treatment for schizophrenia, cognitive or bipolar disorder; severe untreated proliferative retinopathy; current use of oral corticosteroids or suffering from a condition which necessitated oral or systemic corticosteroid use more than once in the previous 12 months; substance abuse, other than nicotine; a history of cancer, excluding well differentiated thyroid carcinoma, breast carcinoma without lymph node metastases, and skin carcinoma; and plans to engage in activities that require going >25 feet below sea level.

**Study Design:** The study has a crossover, randomized design and was conducted at a single center (Isala Clinics, Zwolle, The Netherlands). The study consisted of 4 phases: the qualification phase, the first treatment phase, the crossover phase, and the second treatment phase. During the three month qualification phase, the patients’ pre-study diabetic therapy was used to attempt optimization of their glycemic control. The patients were then randomly allocated to one of two groups, which differed only in the sequence of the two therapies. Randomization was performed in blocks of 4.

Insulin (U400 semi synthetic human insulin of porcine origin; Hoechst, Frankfurt, Germany, recently Sanofi-Aventis) was administered with an implanted pump (MIP 2007C, Medtronic/Minimed, Northridge, CA, USA). The CIPII pump was implanted under
Glycemic control with IP versus SC insulin

Figure 1 is a schematic representation of the pump and its location. For subjects who received SC insulin during the second treatment phase, the CIPII pump was filled with an inert fluid at the end of the first treatment phase. SC insulin was delivered with either MDI or CSII, according to what was used prior to the study. Both treatment phases were 6 months in duration. A crossover phase of 4 weeks was instituted in between to minimize carryover effects of CIPII. During the crossover phase, insulin was administered subcutaneously.

After completion of the trial, subjects were given the option of continuing with their preferred mode of therapy.

Patients monitored their own glucose levels (SMBG; One Touch Ultra, LifeScan, Milpitas, CA, USA) four times every day (fasting, before meals, bedtime), and 7 times daily 2 days per week (fasting, before and after meals, bedtime). If nocturnal hypoglycemia was suspected, subjects would perform an additional blood glucose measurement between 2 and 3 A.M. Furthermore, subjects recorded all episodes of hypoglycemia grade 1, defined as glucose <4.0 mmol/L, grade 2, defined as glucose <3.5 mmol/L, and grade 3, which is defined as the patient requiring third party help and/or losing consciousness, or requiring intravenous glucose or glucagon treatment. To limit the risk of data-entry error, the data from the SMBG meters were downloaded to a computer during every clinic visit.

Twice per month, the study subjects were in contact with a nurse specialized in diabetes, alternating telephone and clinic visits. The subjects were in contact with the medical team as necessary.

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. During all study visits, the 7-point glucose readings were used to adjust the dose regimen if necessary to achieve pre-prandial glucose levels between 4.0-7.0 mmol/L and post-prandial levels between 4.0-9.0 mmol/L.

The study was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients, and the protocol was approved by the Medical Ethics committee of the Isala Clinics in Zwolle.

Measurements: Demographic and clinical parameters were recorded at baseline. These data included smoking and alcohol habits; year of diagnosis of diabetes; the presence of complications; any co-morbidity; and height and weight. The HbA1c level was measured at baseline, at the end of the qualification phase, and at the start, halfway and at the end of both treatment phases with a Primus Ultra2 using high-performance liquid chromatography (reference value 4.0-6.0%). In addition, 5-7 day 24-hour blood glucose profiles were recorded with a continuous glucose monitoring (CGM) system (CGMS, Medtronic/Minimed, Northridge, CA, USA) at baseline, at the halfway point and at the end of both treatment phases. Time spent in the hypoglycemic range was defined as percentage of CGM recordings of <4.0 mmol/L; time spent in euglycemic range was defined as percentage of CGM recordings from 4.0 to 10.0 mmol/L, and time spent in hyperglycemic range was defined as percentage of CGM recordings >10.0 mmol/L.

Primary and secondary outcomes: The primary outcome was the incidence of hypoglycemic episodes. The secondary outcome was glycemic control (as indicated by HbA1c levels). Other pre-specified outcomes included time spent in hypo-, eu-
and hyperglycemia, daily insulin usage, adverse events, and device complications.

Adverse events of CIPII and device complications were subdivided according to the following categories: Pump-malfunction, including catheter obstruction; pump-site infection, defined as a culture proven infection in the subcutaneous pocket of the insulin pump; prolonged pain, defined as pain at the pump-site, which lasted for more than 6 weeks after surgery; cutaneous erosion of the skin, defined as redness with signs of imminent perforation of the overlying skin at the pump-site; postoperative hematoma, defined as a swelling at the pump-site caused by (re)bleeding.

**Statistical analysis:** The incidence of hypoglycemia grade 1 in potentially eligible patients at our clinic of 3.7±2.2 per week was used for sample size calculation. To be able to detect a 30% decrease in hypoglycemic events with a power of 0.80 and a two-sided alpha of 0.05, 34 patients would be needed. To compensate for non-evaluable patients, the initial goal was to enroll 40 patients.

Descriptive summaries included the mean (± standard deviation (SD) or standard error (SE)) for normally distributed variables and the median with the interquartile range (IQR) for other variables. Time variables, such as times spent in the different glycemic states are presented as absolute values. Normality was examined using Q-Q plots. Planned analyses were conducted to address the study objectives as defined, using a nominal significance level of 0.05. General linear models were used to test differences, taking the order of the two treatments into account. To calculate the mean difference with a 95% confidence interval (CI) the Hills-Armitage approach was used (14), which accounts for any period effect (15). If assumptions for the general linear models were not met, non-parametric tests were used, without obtaining a 95% CI. Statistical analyses were performed with SPSS software, versions 15.0 and 16.0. All reported P values are two-sided.

**RESULTS**

**Patients:** Of 50 patients who were screened, 25 entered the qualification phase, after which 1 patient was excluded as having attained acceptable glycemic control. Therefore, 24 patients were randomized and started the first treatment phase between June 2006 and March 2007; 12 patients were assigned to start with SC insulin and 12 patients to start with CIPII during the first phase (Figure in Appendix which is available at http://care.diabetesjournal.org).

The patient characteristics are listed in Table 1. The mean age was 43.6±11.8 years, and the mean diabetes duration was 22.6±10.6 years. The mean numbers of hypoglycemic events grades 1 and 2 were 4.0±2.7 and 2.7±1.9 per week, respectively. The mean HbA1c level was 8.6±1.1%.

One patient withdrew consent during the first treatment phase while on CIPII because of admission to a psychiatric hospital due to a depressive disorder. The patient chose to continue CIPII treatment after withdrawal from the trial, as did all the patients who completed the study.

**Outcome: Hypoglycemia** - The rate of hypoglycemia grade 1 with CIPII was 3.5±2.3 per week compared to 4.0±2.6 per week during SC insulin treatment (mean difference: -0.50 (95%CI:-1.16, 0.17)) (Table 2).

The rate of hypoglycemia grade 2 was 2.3±1.7 per week with CIPII compared to 2.7±1.9 per week during SC insulin treatment (mean difference: -0.43 (95%CI:-0.89, 0.04)). Two episodes of hypoglycemia grade 3 occurred during CIPII treatment and five episodes during SC treatment (all in a single patient).

**Glycemic control** - HbA1c decreased with CIPII from 8.6±1.1% to 7.5±0.7% after 3 months and remained stable at 6 months (7.5±0.9%). During SC treatment there was
no change in glycemic control (Figure 2). When taking the effect of the treatment order into account, HbA1c improved -0.76% (95%CI:-1.41,-0.11) with CIPII compared to SC insulin treatment (absolute values; Table 2). The effect of treatment order was 0.37 (95%CI:-0.28, 1.02) after 6 months.

**Glucose profile (CGM recording)** -
The time spent in hypoglycemia was not significantly different between CIPII and SC treatment (-2.0% (95%CI:-5.4, 1.3)). However, the time spent in euglycemia was 10.9% more with CIPII compared to SC treatment (95%CI: 4.6, 17.3). Subjects spent -8.9% (95%CI:-16.7,-1.1) time in hyperglycemia with CIPII compared to SC insulin treatment (Table 2, Figure 3).

**Insulin usage and clinical parameters** -
There were no significant differences between CIPII and SC insulin treatment with respect to daily insulin usage and clinical parameters (Table 2).

**Adverse events and device complications** -
There were no incidences of intraperitoneal pump or catheter malfunction. One subject developed a postoperative pump pocket hematoma requiring surgical drainage, but neither insulin delivery nor its action was affected. In 3 subjects, prolonged pain occurred, which was successfully treated with oral analgesics (n=2) and relocation of the catheter (n=1).

During the crossover phase, after receiving SC insulin, 1 patient was diagnosed with myocardial ischemia and subsequently treated with coronary artery bypass grafting. After an extension of the crossover phase, this subject continued with the trial.

**CONCLUSIONS**

With CIPII there was no significant decrease in the number of hypoglycemic events. Nevertheless, treatment with CIPII did reduce HbA1c levels by 0.76% compared to SC insulin (absolute value). The improvement in HbA1c was accompanied by an increased time spent in euglycemia and less time spent in hyperglycemia, both without any increase in either daily insulin dose or BMI. At the end of the study, all patients opted to continue with CIPII.

Haardt et al. performed a randomized study comparing CIPII in a crossover manner with SC human insulin by MDI in 9 patients with type 1 diabetes (16). They reported a 1.3% difference in HbA1c levels after 6 months in favor of CIPII as well as a reduction in glucose variability and hypoglycemic episodes when treating with CIPII (16). The only other randomized controlled trial comparing CIPII with SC insulin in patients with type 1 diabetes (n=21) had a parallel design, and found no difference in HbA1c levels (17). Since these two studies were published, insulin analogues with more physiological profiles have become widely available, and when used in CSII improve glycemic control (18-23). No randomized trial comparing regimens based on insulin analogues with CIPII has been previously published. A 45-day retrospective open label trial in 14 patients with type 1 diabetes compared CIPII with CSII using insulin Lispro, and reported a 0.5% lower average HbA1c with CIPII (24).

One major limitation is that due to budget constraints, we were only able to include 24 patients in our study, instead of the projected 40, which severely reduced the statistical power. Furthermore, four patients used MDI instead of CSII in the control phase which may have affected the results. Another possible source of bias that we tried to minimize by using a crossover design is the influence of subject preferences and expectations.

Taking recent price increases into account, it is not likely that this treatment option will be cost effective in the near future, although a formal cost benefit analysis has not been done.
Based on our results, we recommend considering CIPII as a treatment option for those patients with type 1 diabetes who fail to reach satisfactory glycemic control on other intensive insulin treatment regimens.

ACKNOWLEDGEMENTS
The authors would like to thank Harma Israël and Anita van Linde for their help with conducting the study. Furthermore, the authors acknowledge Medtronic for their financial support.

Disclosure: The authors have no financial or other relationships that might lead to a conflict of interest. The sponsor had no role in the study design, data collection, analysis, interpretation, or the writing of the report.
REFERENCES
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=24)</th>
<th>CIPPII (n=12)</th>
<th>SC insulin (n=12)</th>
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<tr>
<td>Male sex</td>
<td>11 (46%)</td>
<td>6 (50%)</td>
<td>5 (42%)</td>
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<tr>
<td>Age (years)</td>
<td>43.6 ± 11.8</td>
<td>43.3 ± 11.9</td>
<td>43.9 ± 12.2</td>
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<td>Diabetes duration (years)</td>
<td>22.6 ± 10.6</td>
<td>20.6 ± 9.5</td>
<td>24.7 ± 11.6</td>
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<td>Current smoker (%)</td>
<td>5 (21%)</td>
<td>2 (17%)</td>
<td>3 (25%)</td>
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<td>Systolic blood pressure (mm Hg)</td>
<td>138.5 ± 21.8</td>
<td>141.5 ± 20.2</td>
<td>135.5 ± 23.7</td>
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<td>Diastolic blood pressure (mm Hg)</td>
<td>80.1 ± 7.8</td>
<td>82.7 ± 6.5</td>
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<td>Body weight (kg)</td>
<td>81.5 ± 15.7</td>
<td>81.3 ± 18.0</td>
<td>81.8 ± 13.9</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>26.4 ± 4.7</td>
<td>26.3 ± 5.3</td>
<td>26.4 ± 4.3</td>
</tr>
<tr>
<td>Hypoglycemia during qualification phase (n/wk) *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>4.0 ± 2.7</td>
<td>4.1 ± 2.9</td>
<td>3.8 ± 2.7</td>
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<tr>
<td>Grade 2</td>
<td>2.7 ± 1.9</td>
<td>2.8 ± 1.8</td>
<td>2.6 ± 2.0</td>
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<td>Time spent in glucose range (%) †</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>8.1 ± 7.7</td>
<td>7.2 ± 6.9</td>
<td>9.0 ± 8.6</td>
</tr>
<tr>
<td>Euglycemia</td>
<td>45.2 ± 12.6</td>
<td>44.2 ± 10.6</td>
<td>46.1 ± 14.8</td>
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<tr>
<td>Hyperglycemia</td>
<td>46.7 ± 18.0</td>
<td>48.6 ± 15.2</td>
<td>44.9 ± 20.9</td>
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<td>HbA₁c (%)</td>
<td>8.6 ± 1.1</td>
<td>8.5 ± 1.0</td>
<td>8.6 ± 1.2</td>
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<td>Previous mode of insulin therapy</td>
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<tr>
<td>CSII</td>
<td>20 (83%)</td>
<td>11 (92%)</td>
<td>9 (75%)</td>
</tr>
<tr>
<td>MDI</td>
<td>4 (9%)</td>
<td>1 (8%)</td>
<td>3 (25%)</td>
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<tr>
<td>Insulin dose during qualification phase (IU/day)</td>
<td>46.3 (35.5, 70.2)</td>
<td>44.1 (35.8, 80.0)</td>
<td>47.0 (35.1, 56.2)</td>
</tr>
</tbody>
</table>

Data are n (%) or mean ± SD or median (interquartile range). CIPPII = continuous intraperitoneal insulin infusion; SC = subcutaneous; BMI = body mass index; CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injections.

* Hypoglycemia grade 1 is defined as blood glucose value < 4.0 mmol/L, hypoglycemia grade 2 is defined as blood glucose value < 3.5 mmol/L. † Time spent in hypoglycemia is defined as percentage of continuous glucose monitoring (CGM) recordings of <4.0 mmol/L, time spent in euglycemia is defined as percentage of CGM recordings between 4.0-10.0 mmol/L and time spent in hyperglycemia is defined as percentage of CGM recordings >10.0 mmol/L.
Table 2. Change per treatment mode and overall CIPII treatment effect

<table>
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<th>Characteristic</th>
<th>Treatment mode</th>
<th>Treatment Effect adjusted for treatment order *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CII (n=23)</td>
<td>SC insulin (n=23)</td>
</tr>
<tr>
<td></td>
<td>Change</td>
<td>Change</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>-0.73 ± 1.25</td>
<td>0.05 ± 0.54</td>
</tr>
<tr>
<td>Hypoglycemia grade 1 (n/wk) †‡</td>
<td>-0.64 ± 2.11</td>
<td>-0.15 ± 1.33</td>
</tr>
<tr>
<td>Hypoglycemia grade 2 (n/wk) †‡</td>
<td>-0.49 ± 1.68</td>
<td>-0.07 ± 1.07</td>
</tr>
<tr>
<td>Time spent in glucose range (%)†§</td>
<td>-3.0±6.2</td>
<td>-1.3±8.3</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>7.8±18.9</td>
<td>-4.1±17.2</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>-4.7±22.0</td>
<td>5.4±19.5</td>
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<tr>
<td>Insulin dose (IU/day) †</td>
<td>0.5 (-6.8, 5.0)</td>
<td>0.3 (-6.7, 5.8)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg) †</td>
<td>0.4±17.6</td>
<td>-4.0±16.3</td>
</tr>
<tr>
<td>BMI (kg/m²) †</td>
<td>-0.4±1.2</td>
<td>0.2±0.9</td>
</tr>
</tbody>
</table>

Data for change are mean ± SD or median (interquartile range). CIPII = continuous intraperitoneal insulin infusion; SC = subcutaneous; CI = confidence interval; BMI = body mass index;
* Mean differences with 95% CI adjusted for treatment order are calculated using the Hills-Armitage method (14). † Change from baseline is reported. ‡ Hypoglycemia grade 1 is defined as blood glucose value < 4.0 mmol/L, hypoglycemia grade 2 is defined as blood glucose value < 3.5 mmol/L. § Time spent in hypoglycemia is defined as percentage of continuous glucose monitoring (CGM) recordings of <4.0 mmol/L, time spent in euglycemia is defined as percentage of CGM recordings between 4.0-10.0 mmol/L and time spent in hyperglycemia is defined as percentage of CGM recordings >10.0 mmol/L.
**Title/Legend Figure 1:** Schematic view of the position of the insulin pump and catheter in vivo

**Title Figure 2:** Glycated Hemoglobin  
**Legend Figure 2:** Mean HbA1c (%) at baseline and during subcutaneous (SC) insulin therapy (grey lines) and intraperitoneal insulin (IP) therapy (black lines). * p<0.05 between therapy groups (solid lines). Dashed lines indicate HbA1c in the 2 treatment order groups; smallest dashes indicate SC insulin first, CIPII second group; larger dashes indicate CIPII first, SC insulin second. The I bars represent standard errors.

**Title Figure 3:** Time spent in different glucose ranges  
**Legend Figure 3:** Mean (SE) time spent in hypoglycemic range (<4.0 mmol/L; panel A), euglycemic range (4.0-10.0 mmol/L; panel B) and hyperglycemic range (>10.0 mmol/L; panel C) at baseline (grey bars) and during subcutaneous insulin therapy (white bars) and intraperitoneal insulin therapy (black bars). * p<0.05 between therapy groups.

**Title Figure Appendix:** CONSORT (Consolidated Standards of Reporting Trials) flowchart  
**Legend Figure Appendix:** Flowchart. IP = intraperitoneal; SC = subcutaneous.
Glycemic control with IP versus SC insulin
Glycemic control with IP versus SC insulin