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## Original Article

# Effects of insulin pump vs. injection treatment on quality of life and impact of disease in children with type 1 diabetes mellitus in a randomized, prospective comparison

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Objective: Effects of pump treatment vs. four times daily injections were explored in children with diabetes with regard to quality of life and impact of disease as well as adverse effects and parameters of metabolic control.
Methods: An open, parallel, randomized controlled prospective comparative study lasting 14 months was completed by 38 type 1 children with diabetes (age 4–16 yr) following a 3.5-months run-in phase. Standardized quality-of-life Pediatric Quality of life Inventory (PedsQL) and impact of disease scores were obtained every 3.5 months as well as regular medical parameters. Parallel treatment group data and longitudinal within-patient data were analysed for each treatment modality.
Results: Within-patient comparisons of the two treatment modalities showed significant improvement in PedsQL and impact scores after pump treatment. Treatment group comparisons did not show significant improvement. Pump treatment resulted in decreased symptomatic hypoglycaemia and lowered haemoglobin A1c by 0.22% after run in.
Conclusions: Within-patient comparison suggests that metabolic control, frequency of severe hypoglycaemia (a threefold decrease), quality of life and impact of disease scores are improved by pump treatment in comparison to regular treatment with four daily insulin injections.

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More than 1000 children have been enrolled over time in either retrospective or non-randomized prospective follow-up studies of continuous subcutaneous insulin infusion (CSII) (1), some of which indicate a lasting decrease of haemoglobin A1c (HbA1c) (2, 3). These studies show that CSII is safe for use in children, resulting in less hypoglycaemia and better HbA1c, with some 30% lower daily insulin doses than when multiple daily insulin injections (MDII) are applied. CSII was considered beneficial by children and parents alike as they experienced more treatment flexibility and comfort (4, 5) than with daily injections.

However, almost all these studies focused on metabolic control rather than on parameters for quality of life or impact of disease. Furthermore, only five randomized comparisons have been published in children comparing MDII, mostly four times daily, with insulin pump therapy (CSII) (5–9), three of which were in preschoolers (7–9). In contrast to non-randomized surveys, only one of those reported a significantly lower HbA1c with CSII (6). None of the randomized paediatric studies was preceded by a proper run-in phase (10).

The aim of the present study was to investigate the changes in quality of life and of impact of disease by either CSII or MDII prospectively in a randomized study preceded by a 3.5-month run-in phase of MDII, following medical effects simultaneously.

## Methods

### Patients

Study participation was sought in our own clinic and nationwide by announcement in the Dutch Diabetes Association's monthly news bulletin. Thirty-nine patients were enrolled in 11 months time, 20 from our own clinic and 19 referred for the duration of the investigation. For 35 children (90%), both parents were of Caucasian origin. None of the children had used an insulin pump before for any length of time. Our clinic had insulin pump experience since 1983, and at the time of this study, 35% of the 120 children were on insulin pumps. Ten of the 39 patients included sought participation in the study because of frequent severe hypoglycaemias (>4/year during the previous year), severe hypoglycaemia defined as any hypoglycaemic event requiring assistance from another person or resulting in seizure or coma. Another six children participated because of severely fluctuating glucose levels with more than 3 weekly symptoms of milder hypoglycaemia and/or capillary blood glucose levels <3.8 mmol, for which ingestion of extra carbohydrates was deemed necessary. The remaining 23 children were included solely because of consistent HbA1c levels above 8%.

Inclusion criteria were type 1 diabetes, diagnosed by the presence of islet antigen-2, glutamic acid decarboxylase-65 or islet cell cytoplasmic autoantibodies, daily insulin administration for 1 yr or longer, random C-peptide <200 pmol, HbA1c > 8.0%, a history of repeated symptomatic hypoglycaemias, age 4–16 yr, and attendance of a regular school. Exclusion criteria were clinically manifest chronic complications, pregnancy, co-morbidity, mental retardation, psychiatric treatment or symptoms in a child or a parent, insufficient Dutch language capabilities and absence of a telephone at home.

The study protocol was approved by the Erasmus University Medical Centre/Sophia Children's Hospital's Medical Ethical Technical committee. Written consent was obtained from both parents and the children if older than 12 yr prior to the study.

### Study design

An open-label, randomized, prospective parallel design was chosen to compare MDII with CSII (Fig. 1). All management was on an out-patient basis. All measurements, medical and psychological, were performed at 3.5 month ± 1 wk intervals. The Pediatric Quality of life Inventory (PedsQL 4.0, Dutch version) (11) was taken from all parents and from 37 of the 39 participating children older than 5 yr. Disease impact scores were obtained from parents only, using the Diabetes Quality of Life Questionnaire and omitting the last 4 of the total of 23 impact questions, those that are designed for children (12, 13). The interviews and resulting scores were obtained by a single psychologist every 3.5 months.

The study design included a 3.5-month run-in phase on MDII for all children, consisting of injecting three short-acting insulin doses s.c. before breakfast, lunch and supper. During MDII, 26 children used insulin aspart and 12 used regular insulin before meals. At bedtime, longer acting s.c. insulins were given, 23 using intermediate-acting insulin neutral protamine Hagedorn (NPH) and 15 insulin glargine. One child dropped out after the run-in phase. For CSII, only insulin aspart was used. The diabetes team was available 24 h/d for consultation by telephone. Results of home blood glucose monitoring three to four times daily were noted in booklets throughout the study. New and carefully calibrated Precision Xtra (Abbott, Alameda, CA, USA) equipment was used for capillary blood glucose measurement. Individualized insulin doses and dietary adaptations were provided in writing for each child and each child's parents at each 5- to 6-wk clinic visit throughout the study, the target blood glucose level being 4–10 mmol. All patients were instructed to count carbohydrates. Dietary advice was given every 3.5 months, based on written nutritional intake and

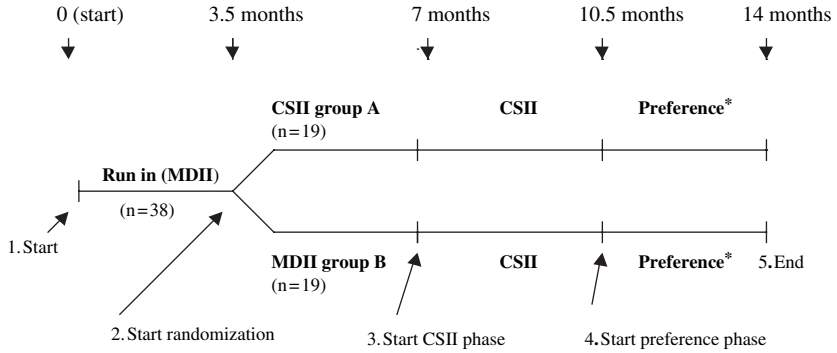


*Fig. 1.* Flowchart of the randomized parallel trial design over time. Subjects in the two arms were followed during 3.5-monthly intervals. Group A switched from multiple daily insulin injections (MDII) to continuous subcutaneous insulin infusion (CSII) at 3.5 months after the start of the study. Group B followed after 7 months. *CSII phase because all patients chose to continue CSII.

exercise reports 3 d before the visit. Injection sites were checked at all visits and rotation advised accordingly with intensive out-patient guidance, including the 24-h telephone service. For CSII H-tron Disetronic insulin pumps (Roche, Basel, Switzerland) were used, changing the infusion catheter every 2 d. CSII insulin dosage was initiated as 75% of the total daily MDII dose, mostly 50% as basal insulin day and night and 50% premeal, including snacks.

After the 3.5 months of run-in phase, each child was randomly assigned to either (ongoing) MDII or CSII using the 'closed envelop' method, supplied by the Public Health Department. Comparison between MDII and CSII was performed during 3.5 months, thereafter all children continued with CSII for another 7 months by unanimous preference. As shown in Fig. 1, after run in, the choice of a parallel design for MDII vs. CSII comparison resulted for group A children in 10.5-month CSII treatment and for group B children in 3.5-month MDII, followed by 7-month CSII treatment.

Capillary blood samples were sent to the national standardization laboratory for determination of HbA1c by high-performance liquid chromatography [Dutch: SKZL, Winterswijk, the Netherlands, head Dr C Weijkamp (IFCC)]. The HbA1c level in patients without diabetes is 4.5–6.0% (14).

### Statistical analysis

All data from the 38 children completing the studies were analysed at baseline and at 3.5-monthly follow-ups. Baseline characteristics were compared by Levine's independent *t*-tests. Parallel data were available from 19/38 children (Fig. 1) for the two randomized treatment arms, CSII (group A) and MDII (group B). The data from these were compared by baseline-adjusted repeated measures ANOVA with random intercepts. Within-patient CSII data available from all 38 children – over 10.5 months for group A and 7 months of CSII for group B – between initiation of CSII and completion of the (unanimous) CSII preference phase were compared using paired *t*-tests. This time-span was chosen as the longest available. The level of significance was set at $p < 0.05$ for all comparisons.

## Results

Of the 39 children enrolled, 38 completed the study. One 11-yr-old girl consistently refrained from the pump phase of CSII after 3 wk because of its visibility on the beach. Of the 38 children completing the study, 9 were aged 4–7 yr, 22 were 8-12 yr and 7 were 13–16 yr. Table 1 shows the baseline characteristics of the children randomly assigned to group A (CSII) and group B (MDII).

Table 2 contains the numerical data of ensuing results of each study phase indicated by 1–5.

The upper part (group A 1–5 and group B 1–5) shows the results of treatment group analyses, with above the results for group A, i.e., the children assigned by parallel randomization to 3.5-months CSII, and below those for group B, assigned to (ongoing) 3.5-months MDII prior to CSII.

The lower part of Table 2 contains the data obtained for the within-patient analysis of children having used CSII during any of the study phases 1–5: 10.5 months for group A and 7 months for group B children as a result of the parallel design of the study (Fig. 1).

### Adverse events

During MDII (Fig. 1), covering almost 17 patient years in total, a high number of severe hypoglycaemias still occurred, averaging 1.1 per patient year (group A was on MDII for 3.5 months and group B was on MDII for 7 months, altogether almost 17 patient years). During CSII, covering almost 28 patient years in total, severe hypoglycaemia decreased to an average of 0.29 per patient year, indicating a more than threefold reduction of severe hypoglycaemia events. In the 3.5 months of randomization, four severe hypos occurred in the MDII group and two in the pump group. Admission for ketoacidosis occurred four times for patients on MDII (all in adolescents aged >12 yr) and two times for one patient on CSII (an adolescent aged 14 yr).

### Quality of life and impact of disease

The PedsQL scores (38 parents and 36 children aged >5 yr) increased significantly during the run-in phase ($p = 0.006$ for parents and $p = 0.001$ for children). PedsQL scores remained stable while on MDII in the randomization phase and increased non-significantly

Table 1. Baseline characteristics by randomization group

| | Group A (CSII) | Group B (MDII) |
|---|---|---|
| Age (yr) | 10.0 ± 3.0 | 10 ± 3.7 |
| n (number of female) | 19 (12) | 19 (9) |
| Duration (yr) | 5.6 ± 3.3 | 4.7 ± 2.9 |
| BMI SDS† | 0.51 ± 0.84 | 0.29 ± 0.95 |
| HbA1c % start run in | 8.26 ± 0.80 | 8.40 ± 1.06 |
| HbA1c % after run in | 7.66 ± 0.56 | 7.98 ± 0.57 |
| Daily insulin dose (U/kg/d)* | 0.98 ± 0.21 | 1.10 ± 0.44 |
| PedsQL, parents | 78.3 ± 10.2 | 74.5 ± 13.4 |
| PedsQL, children | 79.4 ± 11.3 | 79.2 ± 9.5 |
| Impact score, parents | 46.2 ± 8.7 | 42.7 ± 8.8 |

CSII, continuous subcutaneous insulin infusion; MDII, multiple daily insulin injections; PedsQL, Pediatric Quality of life Inventory.
Data are presented as mean ± SD. No significant differences were found for types of insulin used during the run-in phase.
*$p = 0.029$.
†Body mass index standard deviation score (BMI SDS) according to Dutch reference, 1997 (15).

Table 2. Outcome measures for group A (CSII) and group B (MDII)

| Variable | Impact score, parents | PedsQL Children | PedsQL Parents | HbA1c | Insulin (U/kg/d) |
|---|---|---|---|---|---|
| Cross-sectional analysis | | | | | |
| Group A (CSII) (n = 19) | | | | | |
| 1. Start | 46.2 ± 8.7# | 79.4 ± 11.4 | 78.3 ± 10.2# | 8.26 ± 0.80# | 0.98 ± 0.21 |
| 2. After run in | 42.8 ± 7.8* | 86.0 ± 9.5 | 82.5 ± 8.9* | 7.66 ± 0.56* | 1.03 ± 0.22# |
| 3. After random (CSII) | 40.2 ± 8.5 | 88.8 ± 9.0 | 86.2 ± 6.1 | 7.49 ± 0.50 | 0.71 ± 0.13* |
| 4. After CSII | 40.5 ± 9.8 | 87.8 ± 9.9 | 83.7 ± 10.7 | 7.53 ± 0.67 | 0.74 ± 0.12 |
| 5. After CSII | 38.8 ± 8.0 | 89.6 ± 9.3 | 85.3 ± 11.8 | 7.53 ± 0.55 | 0.76 ± 0.15 |
| Group B (MDII) (n = 19) | | | | | |
| 1. Start | 42.7 ± 8.8 | 79.2 ± 9.5 | 74.5 ± 13.4# | 8.41 ± 1.07# | 1.10 ± 0.44 |
| 2. After run in | 41.9 ± 8.4 | 81.9 ± 11.6 | 78.6 ± 12.5* | 7.98 ± 0.57* | 1.07 ± 0.32 |
| 3. After random (MDII) | 40.6 ± 9.5# | 82.3 ± 12.8# | 79.7 ± 12.2# | 7.97 ± 0.78 | 1.07 ± 0.32# |
| 4. After CSII | 36.7 ± 7.8* | 86.1 ± 10.5* | 84.9 ± 10.8* | 7.76 ± 0.90 | 0.77 ± 0.17* |
| 5. After CSII | 37.6 ± 8.7 | 85.0 ± 13.3 | 85.5 ± 12.9 | 7.65 ± 0.88 | 0.78 ± 0.20 |
| Within-patient analysis | | | | | |
| All children (n = 38) | | | | | |
| 1. Start | 44.5 ± 8.8 | 79.3 ± 10.3# | 76.4 ± 11.9# | 8.34 ± 0.93# | 1.04 ± 0.35 |
| 2. After run in | 42.4 ± 7.8 | 84.0 ± 10.7* | 80.6 ± 10.9* | 7.82 ± 0.58* | 1.05 ± 0.27 |
| 2/3. Start CSII† | 41.7 ± 8.7# | 84.1 ± 11.3# | 81.1 ± 10.6# | 7.81 ± 0.69# | 1.04 ± 0.29# |
| 5. End of study | 38.2 ± 8.3* | 87.3 ± 11.6* | 85.4 ± 12.2* | 7.59 ± 0.73* | 0.77 ± 0.18* |

CSII, continuous subcutaneous insulin infusion; MDII, multiple daily insulin injections; PedsQL, Pediatric Quality of life Inventory.
*$p < 0.05$, compared with the phase of the study mentioned one line above and marked with a #.
†Start of CSII for group A (2) and for group B (3); hence, group A was on CSII for 10.5 months and group B for 7 months.

by 2.5 points on average while on CSII (Table 2, upper part, columns 3 and 4, rows 4 and 5). After completion of the randomization, all 38 children were on CSII by preference with both PedsQL scores, maintaining a level at an average of 10 points (85–90) higher than that at baseline (75–80).

By contrast, within-patient analysis during CSII involving 38 children during 7–10.5 months (Table 2, lower part, columns 3 and 4) showed an increase of the child-reported PedsQL scores from 84.1 ± 11.3 to 87.3 ± 11.6 ($p = 0.023$) and an increase in parent-reported PedsQL scores from 81.1 ± 10.6 to 85.4 ± 12.2 ($p = 0.025$).

The impact of disease score (Table 2, lower part, column 2) in the run-in phase decreased non-significantly from 44.5 ± 8.8 to 42.4 ± 7.8 ($p = 0.058$) and also non-significantly during the randomization phase. As with the PedsQL score, the within-patient analysis (Table 2, lower part, column 2) showed a significant decrease in impact of disease from 41.7 ± 8.7 to 38.2 ± 8.3 ($p = 0.0063$).

### Glycaemic control

HbA1c significantly decreased in the run-in phase for all 38 participating children (Table 2, lower part, column 5, rows 16 and 17) from 8.34 to 7.82. (−0.52%, $p = 0.001$). Fifteen children used glargine insulin at bedtime and the other 23 children NPH insulin, but no significant differences were found in their HbA1c (%). No differences were seen in HbA1c between the 12 regular insulin users and the 26 insulin aspart users before meals.

A non-significantly but marked difference was seen between the HbA1c at the start of the study between the referred children (n = 19) and the children from our centre (n = 19) (HbA1c 8.53 vs. 8.14%, $p = 0.2$). However at the start of the randomization phase, no significant differences were seen between the referred patients and the patients from our centre (HbA1c 7.89 vs. 7.7%, $p = 0.64$).

The within-patient analysis (Table 2, lower part, column 5, rows 18–19) showed a decrease in HbA1c at the end of the 7- to 10.5-month CSII period by 0.22% ($p = 0.02$) while using an average of 0.27 U/kg/d less insulin (Table 2, lower part, column 6, rows 18–19), $p < 0.001$. In keeping with this improvement, the subset of 13 children with HbA1c levels >8% at the start of CSII (mean 9.1 ± 1.0) showed a decrease in HbA1c to a mean of 8.56% ± 1.0 after 7–10.5 months of CSII ($p = 0.01$).

## Discussion

This is the only randomized prospective childhood diabetes treatment study comparing MDII with CSII preceded by an adequate run-in phase. It is telling that only 1 of the 39 children aged 4–16 yr enrolled dropped out from this demanding study lasting 14 months. However, no significant ($p < 0.05$) improvement was found in PedsQL nor in impact of disease scores during the actual randomization phase when children in the MDII condition were directly compared with those in the CSII condition.

During run-in phase, PedsQL and impact of disease scores improved significantly and so did HbA1c (from

8.34 to 7.82%). It seems that these effects were 'stolen' from the subsequent randomization phase comparing MDII with CSII, which might explain the more positive reports on childhood direct MDII vs. CSII comparisons without run in reported in other studies (6, 16–19). A significant study effect could be caused by either suboptimal treatment prior to the study or suboptimal CSII treatment during the study proper. The 19 children who were referred to our clinic did show a more pronounced decrease in HbA1c compared with the 19 children enrolled from our clinic (0.64 vs. 0.44%).

The study design allowed for a within-patient analysis looking into the effects of CSII for 7.5–11 months in all 38 participants. In this comparison, PedsQL scores obtained from children and parents improved and impact of disease scores obtained from parents decreased significantly. One explanation for this difference is statistical. Variance in scores by two-way ANOVA (treatment group) will be larger than those by paired *t*-tests (within patient). HbA1c improved by 0.22%. No significant correlations were found between decrease of HbA1c and improvement of quality-of-life parameters. The present HbA1c findings agree with much larger studies in adults using a run-in phase (20). In addition, the current study showed a threefold decrease of severe hypoglycaemia when children were in CSII treatment. The number of hypoglycaemic events per child was however insufficient to test if this is related to improved quality of life and/or lessened impact of disease.

Limitations of our study are the limited power of the study, with 19 patients in each study group and the short duration of the randomization phase, only 3.5 months. Several studies showed that a longer observation period is needed to obtain significant differences between MDII and CSII (2, 3) Also the findings raise the question whether the PedsQL and impact of disease questionnaires used have enough sensitivity to show improvement by CSII over MDII in children of ages varying from 4 to 16 yr. It cannot be excluded that the five repetitive assessments with 3.5-month interval during this study suffered from carry-over effects, although the trends of Table 2 do not support this premise.

In conclusion, a threefold decrease in sever hypoglycaemia was observed in the CSII phase of this study, and quality of life and impact of disease scores were shown to improve by CSII when within-patient analyses were performed but not when treatment groups were compared. Better psychometric tools, higher numbers of participants and longer observation periods preceded by an adequate run-in phase will be needed to definitely show that quality of life is improved and impact of disease is diminished by CSII in childhood diabetes. Such studies are needed to underscore the fact that patients largely prefer CSII over MDII (3, 5, 6, 16, 19).

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