

Original Article

Initiation of insulin pump therapy in children at diagnosis of type 1 diabetes resulted in improved long-term glycemic control

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Background: Insulin pump therapy (IPT) is increasingly used in children and young people with type 1 diabetes. There are limited studies evaluating the optimal time to start IPT.

Objective: The aim of this study was to determine if early initiation of IPT in children with type 1 diabetes leads to improved glycaemic control and quality of life (QOL) compared with the later introduction of IPT.

Subjects: There were 38 subjects in the early pump group (EPG) (age 12.6 + 4.9 yr, 23 male) and 37 in the later pump group (LPG) (age 13.1 + 4.1 yr, 19 male).

Methods: Hemoglobin A1c (HbA1c), rate of severe hypoglycemia, and diabetic ketoacidosis (DKA) were collected retrospectively over a 48-month period. Eligible subjects and/or their parents completed both a Paediatric and Paediatric Diabetes-specific Quality of Life Inventory.

Results: HbA1c measurements were lower in the EPG (6.8%; 51 mmol/mol) compared to the LPG (7.9%; 63 mmol/mol), across the 48 months of the study ($p < 0.0001$). There was no significant difference in the rate (per patient years) of severe hypoglycaemia (0.02; 0.07) $p = 0.075$ between the two groups. There were no episodes of DKA in either group. There was no significant difference in QOL between the groups with both having high satisfaction rates.

Conclusions: Initiation of IPT at diagnosis of type 1 diabetes in children resulted in consistently lower HbA1c with no apparent change in hypoglycemia, DKA, or QOL.

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Key words: children and adolescents – diabetes mellitus type 1 – HbA1c – IPT – QOL

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Insulin pump therapy (IPT) is now considered a standard treatment for type 1 diabetes (1). The advantages of IPT are that it mimics physiologic insulin release better than multiple daily injection (MDI) therapy and allows for greater flexibility in food intake and physical activity (2). In a joint statement by the

European Association for the Study of Diabetes and the American Diabetes Association, IPT is described as ‘a treatment option for adults with type 1 diabetes who are motivated to improve glycemic control following a trial of multiple daily insulin injection (MDI) therapy and who can show the level of self-care required for

adherence' and that the indications were 'broadly similar in children, although in some countries IPT is routinely started at the time of diagnosis' (3). This statement suggests that IPT should only be used after a trial of MDI.

There have, however, been studies of early introduction of IPT. Thraikill et al. (2011) studied 24 patients in whom IPT was commenced within 1 month of diagnosis and showed that IPT was well tolerated, led to improved glycemic control and satisfaction (4). Ramchandani et al. (2006) studied 28 newly diagnosed patients and observed improved glycemic control over 3 yr (5).

The authors previously reported the results of a pilot study which evaluated the impact of IPT on glycemic control in a group of children and adolescents with type 1 diabetes. A small number of these children were commenced on IPT at diagnosis and showed significantly lower hemoglobin A1c (HbA1c) measurements compared to children commenced on IPT later. The improved HbA1c levels were sustained for up to 3 yr (6).

The aim of this study was to determine if early initiation of IPT in children with type 1 diabetes leads to improved glycemic control and quality of life (QOL) compared with the later introduction of IPT.

Methods

This study involved three non-tertiary pediatric practices in south-east Queensland and was a retrospective patient review. The three pediatric practices cared for 107 patients with type 1 diabetes, all of whom were treated on IPT. These practices were not connected other than each pediatrician had significant interest and experience in management of children and young people with type 1 diabetes, expertise in IPT and each practice utilized the same Credentialed Diabetes Nurse Educator to educate both parents and patients on IPT and current diabetes management.

Study subjects

Only subjects aged ≤ 18 yr of age, who commenced on IPT and received their IPT education in one of the three centers were included in the study. Eighty-six of 107 (80.4%) subjects met these criteria. Of these, 11 subjects were excluded because they commenced IPT >30 days and <12 months from diagnosis leaving a study group of 75 (70%) subjects. Subjects who met the inclusion criteria and attended one of the three centers between the 1 January 2007 and the 31 October 2013 were identified and their parents or guardian contacted to ask if their child or young person's data could be used for the study and whether they would complete two QOL survey tools. All 75 parents or guardians

approached agreed to participate and written consent was obtained.

The subjects were assigned to two groups for comparison: the early pump group (EPG) and the later pump group (LPG). The EPG commenced on IPT within 30 days of initial diagnosis while the LPG were those who were on MDI for 12 months or more before being changed to IPT. In the EPG, the 30-day time-frame reflected the time taken for the family to acquire an insulin pump and be educated on its use. The initiation of IPT in the LPG occurred at variable times after 12 months from diagnosis. IPT was commenced if the parents requested it or if glycemic control was suboptimal and IPT was considered the preferred way of improving metabolic control.

Diabetes education

If subjects in the LPG received their initial diabetes education at another center, they underwent re-education of diabetes management as well as management of IPT. The use of one diabetes educator provided a consistent approach to education, target setting for blood glucose and HbA1c levels. Patients also received education from a dietitian including carbohydrate counting. When required, patients and families had access to a mental health professional.

Data

Demographic and clinical data were collected retrospectively from the medical records of the participants for up to 48 months prior to the commencement of the study. Data collected included HbA1c levels, rates of severe hypoglycemia, and diabetic ketoacidosis (DKA), along with other diabetes-related parameters. Severe hypoglycemia was defined as an event leading to loss of consciousness or seizure since commencing IPT. The severity of DKA at presentation was categorized by the degree of acidosis defined by the International Society of Paediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines, 2014 (7, 8), where mild DKA is defined as a pH < 7.3 , moderate is defined as a pH < 7.2 , and severe as a pH < 7.1 . DKA at initial diagnosis was not included in the analysis of events of DKA after commencement of IPT.

Blood glucose monitoring, target, and pump settings

The target blood glucose range for each participant was set between 4 and 5.5 mmol/L with a target HbA1c of $<7.0\%$ (<53 mmol/mol). The insulin to carbohydrate (I:C) ratio and the insulin sensitivity factor (ISF) were individualized for each participant. No patients were

on continuous glucose monitoring (CGMS) during the study period. Subjects were asked to perform a minimum of four blood glucose tests per day.

Analysis of HbA1c data

The participants in the study had an HbA1c measurement every 3 months as part of their routine care. The first 12 months of HbA1c data in the EPG were not analyzed. This was to exclude the impact of the ‘honeymoon’ effect on their glycemic control. For comparison purposes, it was decided not to analyze the first 12 months of HbA1c data for the LPG. Measurements of HbA1c were made using a DCA Vantage™ (Siemens Medical Solutions Diagnostics, Tarrytown, NY, USA), by a quality-certified pathology provider. HbA1c data have been reported in Table 1, in both Systeme International (SI) units (mmols/mol) and National Glycohemoglobin Standardization Program (NGSP) units (%).

Quality of life assessment

Two assessment tools were used to assess QOL: the Paediatric Quality of Life Inventory (PedsQL 4.0) and the type 1 Diabetes Module (PedsQL 3.0) (9). The (PedsQL 4.0) is a modular instrument designed to measure health-related quality of life (HRQOL) in children and adolescents aged 2–18 yr. The type 1 diabetes Module (PedsQL 3.0) was designed to measure diabetes-specific HRQOL. This tool encompasses five scales: (i) diabetes symptoms (11 items), (ii) treatment barriers (4 items), (iii) treatment adherence (7 items), (iv) worry (3 items), and (v) communication (3 items). The format, instructions, Likert-type response scale, and scoring method are identical to the PedsQL 4.0, with higher scores indicating fewer symptoms or problems. QOL questionnaires for children and young people aged ≥ 5 yr were completed by both the child and their parents. For children aged < 5 yr, only the parents completed the questionnaires.

Compliance was assessed during the study period by insulin pump and blood glucose meter downloads. Any non-compliance was addressed and followed up by the diabetes educator.

Statistical analysis

Data were analyzed using statistical program ‘R’ version 3.0.2 (25 September 2013), demographic data are presented as mean \pm standard deviation (SD), body mass index (BMI) as kg/m^2 , and severe hypoglycemia rates were reported as per-patient years. Change in HbA1c was analyzed using an unpaired *t* test. Confidence intervals of 95% and *p* values < 0.05 were considered significant.

Ethics approval was obtained by the Human Research Ethics Committee of the Charles Stuart University, Darwin, Northern Territory (Ethics number H13125).

Results

Subjects

Of the possible 107 subjects, 75 (70%) subjects met the entry criteria for the study with 38 being assigned to the EPG and 37 to the LPG. There was no significant age difference between the two groups with the mean age of subjects in the EPG being 12.6 ± 4.9 yr compared to a mean of 13.1 ± 4.1 yr in the LPG ($p = 0.931$). The mean age at commencement of IPT was also similar with the EPG being 9.0 ± 4.8 yr vs. 8.9 ± 3.4 yr in the LPG ($p = 0.931$). However, there was a significant difference in the mean age at diagnosis. The mean age at diagnosis for the EPG was 9.0 ± 2.0 yr vs. 4.9 ± 2.9 yr ($p \leq 0001$) in the LPG.

Data

Detailed demographics and characteristics of the two groups are shown in Table 1. In the EPG, 22% were commenced on IPT on day 1 of initial diagnosis, 65% were commenced within 6 days, and 13% between 6 and 30 days. There were no episodes of DKA in either group over the 48-month period after commencing IPT. Data on the severity of DKA at diagnosis were analyzed for the EPG (Table 1). However, no data were available for the LPG on DKA at diagnosis. Severe hypoglycemia was reported in 10 (13%) of the 75 subjects with no statistical difference between the EPG ($n = 3$) and the LPG ($n = 7$). There was no significant difference in the total daily insulin requirements between the two groups at Year 1, Year 2, and Year 3 post-pump start. The insulin units/kg/day for the two groups are shown in Table 2. There was also no significant difference between the BMI in the two groups at entry into the study.

HbA1c data

HbA1c data were not analyzed for the first 12 months for either group. However, the mean HbA1c at initiation of IPT in the LPG was 8.8% which decreased to 7.9% (< 0.05) at 12 months. The mean HbA1c at diagnosis in the EPG was 11.2% which had also significantly reduced at 12 months to 6.7% ($p \leq 0.0001$). In both groups, their HbA1c remained below the entry level throughout the course of the study.

The overall glycemic control, as reflected by HbA1c, was lower in the EPG (6.8%; 51 mmol/mol) compared

Table 1. Characteristics and demography of the early and later IPT groups from 12 after initiation of IPT to 48 months

| | Early pump group | Later pump group | p value |
|--------------------------------------|------------------|------------------|---------|
| N (%) | | | |
| All subjects | 38 (51) | 37 (49) | |
| Gold coast | 32 (84) | 19 (51) | |
| Toowoomba | 0 | 10 (27) | |
| Ipswich | 6 (16) | 8 (22) | |
| Age (yr) | 12.6 ± 4.9 | 13.1 ± 4.1 | 0.931 |
| Age (n) | | | |
| Subjects <13 (yr) | 18 | 22 | |
| Subjects ≥13 (yr) | 20 | 15 | |
| Sex | | | |
| Male (%) | 23 (61) | 19 (51) | |
| Female (%) | 15 (39) | 18 (49) | |
| Age at diagnosis (yr) | 9.0 ± 4.8 | 4.9 ± 2.9 | <0.0001 |
| Age at pump start (yr) | 9.0 ± 4.8 | 8.9 ± 3.4 | 0.931 |
| Diabetes duration at pump start (wk) | 0.8 ± 1.0 | 244.4 ± 166.4 | |
| Rate of severe hypoglycaemia* | 0.02 | 0.07 | 0.075 |
| Rate of DKA post-pump start | 0 | 0 | |
| DKA at diagnosis (%) | | | |
| No DKA | 22 (58%) | – | |
| Mild | 6 (16%) | – | |
| Moderate | 2 (5.0%) | – | |
| Severe | 5 (13%) | – | |
| Unknown | 3 (8.0%) | – | |
| BMI at entry (kg/m ²) | 19.7 ± 4.4 | 20.2 ± 3.5 | 0.621 |
| HbA1c (%) and (mmol/mol) | | | |
| HbA1c (n) | 38 | 37 | |
| Overall HbA1c | 6.8 ± 0.89 (51) | 7.9 ± 0.99 (63) | <0.0001 |
| HbA1c subjects <13 (yr) | 6.9 ± 0.88 (52) | 8.0 ± 1.21 (64) | <0.0001 |
| HbA1c subjects ≥13 (yr) | 6.7 ± 0.93 (50) | 7.9 ± 0.73 (63) | <0.0001 |

BMI, body mass index; DKA, diabetic ketoacidosis; HbA1c, hemoglobin A1c; IPT, insulin pump therapy; SD, standard deviation; –, no data.

Unless otherwise stated, demographic data are displayed as a mean ± SD.

*Rate per patient years.

Table 2. Total daily insulin requirements for early and later IPT groups, post-commencement of IPT

| | Early pump group | Later pump group | p value |
|---------------------------------|------------------|------------------|---------|
| Total daily dose (units/kg/day) | | | |
| First year post-IPT | 0.71 ± 0.16 | 0.74 ± 0.17 | 0.96 |
| Second year post-IPT | 0.72 ± 0.16 | 0.76 ± 0.16 | 0.96 |
| Third year post-IPT | 0.76 ± 0.24 | 0.72 ± 0.17 | 0.98 |

IPT, insulin pump therapy; SD, standard deviation.

Displayed as mean ± SD. Units/kg/day displayed as mean ± SD.

to the LPG (7.9%; 63 mmol/mol), $p < 0.0001$. This was also shown at each of the 3 monthly measurements across the 48 months (Fig. 1). However, by the 48-month point, the numbers of participants in both groups were relatively small (EPG 6; LPG 10). The LPG included 6 (16.2%) subjects, in whom IPT was introduced because of poor glycemic control (HbA1c > 9.5%; >80 mmol/mol). All of these subjects experienced a fall in HbA1c across the study period with a prepump mean of 10.7% (93 mmol/mol) which fell to a mean of 7.9% (63 mmol/mol) at 12 months ($p < 0.0001$).

A comparison of HbA1c levels for subjects aged <13 yr and subjects aged ≥13 yr was undertaken in each group. In both age groups, the EPG had significantly lower mean HbA1c [<13 yr, 6.9 vs. 8.0% (52 vs. 64 mmol/mol, $p < 0.01$), ≥13 yr 6.7 vs. 7.9%, (50 vs. 63 mmol/mol), $p < 0.0001$].

Quality of life assessment tools

Of the 75 subjects who consented to participate in the study 61 (81%) completed the QOL survey tools. The completion rate was similar for the two groups: 31/38 (82%) for the EPG and 30/37 (81%) for the LPG. There was no significant difference in QOL measures between the two groups with both groups scoring high levels of satisfaction with their treatment (Table 3).

Discussion

This study demonstrated that children and adolescents who were commenced on IPT within 30 days of diagnosis achieved a mean HbA1c which was 1.1% (12 mmol/mol) lower than for those commenced ≥12

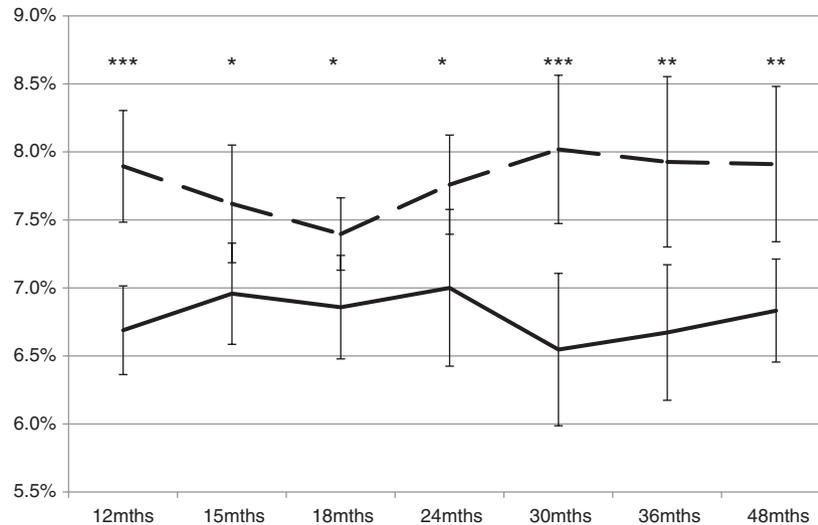


Fig. 1. Comparison of mean hemoglobin A1c (HbA1c) between the two pump groups from 12 months after initiation of insulin pump therapy (IPT) to 48 months. Error bars represent 95% confidence intervals. *p < 0.05, **p < 0.01, ***p < 0.001. Legend — early pump group. - - - - late pump group.

Table 3. Comparison of Quality of Life Inventory total scores between the EPG and LPG

| | Paediatric Quality of Life Inventory (PedsQL 4.0) | | | Diabetes Module Inventory (PedsQL 3.0) | | |
|--------|---|-----|---------|--|-----|---------|
| | EPG | LPG | p value | EPG | LPG | p value |
| Parent | 82 | 78 | >0.5 | 71 | 66 | >0.5 |
| Child | 83 | 80 | >0.5 | 73 | 66 | >0.5 |

EPG, early pump group; LPG, later pump group.

months after initial diagnosis. There was no statistical difference between rates of hypoglycemia, DKA, or QOL between the two groups.

We have demonstrated that it is possible to successfully introduce IPT at diagnosis of diabetes and achieve superior glycemic control over 48 months compared to those commencing IPT ≥ 12 months after diagnosis. In both groups, their HbA1c remained below the entry level throughout the course of the study. Shulman et al. (2012) in a systematic review of the literature observed that while HbA1c levels frequently improve in the first year of treatment, they then trend back toward baseline levels (10). However, it should be noted that the number of participants in each group was relatively small by the 48-month point.

There was a significant difference in the mean age at diagnosis between the two groups with the EPG being older. However, there was no difference in their ages when entered into the study and no age difference at initiation of IPT. The age at diagnosis is important in that older children usually receive primary diabetes education along with their parents. In younger children, the education may only be directed toward the parents and not the child. In our study, each subject who received primary diabetes education at a different

center was re-educated in diabetes management as well as receiving education on IPT. This should have acted to reduce the risk of a knowledge bias between the two groups.

A comparison of HbA1c levels for subjects aged <13 yr and subjects ≥ 13 yr was undertaken as this is around the age when young people become more independent in their diabetes management. In both age groups, the EPG had significantly lower HbA1c levels. Subjects in both groups were required to perform a minimum of four blood glucose measurements per day as it is known that there is a relationship between the number of blood tests undertaken and the HbA1c levels (2).

Although some authors refer to challenges of achieving satisfactory glycemic control in adolescents (11) in our study, the adolescent group’s HbA1c levels were as good as the younger group when IPT was commenced at diagnosis. It is important that the family receive general diabetes education as well as education in the use of IPT when commencing IPT. This education should include dietetic advice and the involvement of a mental health professional (7). The EPG achieved HbA1c results lower than the ISPAD Clinical Practice Guideline (2014) target of <7.5% (<58 mmol/mol) (7). While there were minor fluctuations in HbA1c levels over time within our two groups, the difference in glycemic control was sustained across the 48 months of follow-up. These overall results are similar to, or slightly better than, those of Johnson et al. (2013) who described their study as the largest ever study of IPT in children. In their IPT group, they reported HbA1c results of 7.7–8.1% (61–65 mmol/mol) (11).

Other positive outcomes were the absence of DKA episodes and a low rate of severe hypoglycemic events in

both groups. These outcomes, including the sustained reduction in HbA1c, are similar to the results reported by Johnson et al. (2013) (11). QOL assessment showed a high satisfaction rate in both groups with no significant differences between the groups.

To date, there has been conflicting reports about the benefits of early introduction of IPT. Shalitin et al. (2012) found no added benefit in glyceemic control over time in commencement of early IPT vs. commencing of IPT later (2). Brancato et al. (2014) showed that early IPT commencement resulted in lower and more sustained HbA1c levels than a later commencement (12). Thraikill et al. (2011) reported improved glyceemic control with early IPT and also suggested that early use of IPT may help preserved residual β -cell function (4). However, Buckingham et al. (2013) using sensor-augmented IPT failed to show any benefit on retention of β -cell function (13).

Limitations

The limitations of the study included its retrospective design, the relatively modest number of subjects in each group, especially at the 48 month time-point. Data on the severity of DKA and HbA1c at diagnosis were not readily available for the LPG as many of these subjects had been diagnosed with diabetes at different centers prior to transferring their care to one of the three pediatric practices. We did not collect or report on HbA1c data in the first 12 months after initiation of IPT.

In addition, socioeconomic status was not assessed, but all patients were seen in a private clinic model. The mean duration of diabetes in the LPG prior to commencement in this study was 4.7 yr. C-peptide levels at diagnosis or prior to initiation of IPT were not routinely collected.

Conclusion

Introduction of IPT proximate to the time of initial diagnosis resulted in improved glyceemic control that was achieved with no adverse clinical events or impact on QOL. The improvement in glyceemic control was sustained across the 48 months of the study. We conclude that introduction of IPT at the time of diagnosis is a valid treatment in both the prepubertal and adolescent age groups. These results, whilst promising, need to be confirmed in a larger prospective study which also addresses the limitations of this study consequent to its retrospective design.

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Conflict of interest

The authors declare that there is no duality of interest associated with this manuscript.

Author contribution

D. F. developed the methodology, researched data, data collection, and leader in the discussion, and reviewed and edited the manuscript. E. L. assisted with the development of the methodology, wrote the manuscript, contributed to discussion, and researched data. B. K. contributed to the study design the study design, discussion, and reviewed and edited the manuscript. M. M. researched data and reviewed and edited manuscript. S. D. assisted with the development of the methodology and reviewed and edited the manuscript. D. P. assisted with the development of the methodology, researched data contributed to discussion, and reviewed and edited the manuscript. D. F. is the guarantor of this work and, as such, has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors gave final approval of the version to be published.

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