Continuous subcutaneous insulin infusion versus multiple daily injections in children and young people at diagnosis of type 1 diabetes: the SCIPI RCT

Joanne Blair,[1]* Andrew McKay,[2] Colin Ridyard,[3] Keith Thornborough,[4] Emma Bedson,[2] Matthew Peak,[5] Mohammed Didi,[1] Francesca Annan,[6] John W Gregory,[7] Dyfrig Hughes[3] and Carrol Gamble[2]

[1]Department of Endocrinology, Alder Hey Children's NHS Foundation Trust, Liverpool, UK
[2]Clinical Trials Research Centre, University of Liverpool, Liverpool, UK
[3]Centre for Health Economics and Medicines Evaluation, Bangor University, Bangor, UK
[4]Department of Diabetes, Alder Hey Children's NHS Foundation Trust, Liverpool, UK
[5]Department of Research, Alder Hey Children's NHS Foundation Trust, Liverpool, UK
[6]Paediatric and Adolescent Division, University College Hospital, London, UK
[7]Division of Population Medicine, School of Medicine, Cardiff University, Cardiff, UK

*Corresponding author jo.blair@alderhey.nhs.uk

Declared competing interests of authors: Joanne Blair undertakes paid advisory work for, and has received funding for research, to attend academic meetings and to support a nursing salary from, Novo Nordisk Ltd (Gatwick, UK), a pharmaceutical company that manufactures some of the insulins used in the SubCutaneous Insulin: Pumps or Injections? (SCIPI) study. The work undertaken by Joanne Blair for Novo Nordisk Ltd relates to growth hormone therapy and not diabetes. Mohammed Didi has received payment for advisory work and funding to attend academic meetings and to support a nursing salary from Novo Nordisk Ltd. The work undertaken by Mohammed Didi for Novo Nordisk Ltd relates to growth hormone therapy and not diabetes. Mohammed Didi has received expenses from Merck Serono Ltd (Feltham, UK) to attend educational meetings. Carrol Gamble is a member of the Efficacy and Mechanism Evaluation Programme Board of the National Institute for Health Research. Dyfrig Hughes is a member of the Health Technology Assessment (HTA) Clinical Trials Board (2010–16), the HTA Funding Teleconference (2015–16) and the Pharmaceuticals Panel (2008–12). John W Gregory reports grants from Cardiff University during the conduct of the study, and membership of the HTA Commissioning Board (2010–14). John W Gregory received speaker fees from Pfizer Inc. and Eli Lilly and Company (Basingstoke, UK), fees for attending an advisory board for Eli Lilly and Company and financial assistance to attend annual meetings of the European Society for Paediatric Endocrinology from Sanofi Genzyme (Guildford, UK), Merck Serono Ltd, Ipsen and Novo Nordisk Ltd.

Published August 2018
DOI: 10.3310/hta22420

Scientific summary

Continuous subcutaneous insulin infusion versus multiple daily injections

Health Technology Assessment 2018; Vol. 22: No. 42
DOI: 10.3310/hta22420

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Type 1 diabetes (T1D) is one of the most common chronic diseases of childhood, affecting > 26,000 children and young people in the UK. The daily treatment burden of T1D is high, requiring the administration of subcutaneous insulin in doses calculated according to carbohydrate intake, energy expenditure and blood glucose readings. In the longer term, complications of T1D may result in blindness, renal failure, premature heart disease, stroke and amputation.

The risk of long-term complications of T1D is related to glycaemic control and is lower in patients treated with intensive insulin treatment regimens: multiple daily injections (MDI) (≥ 4 injections) or continuous subcutaneous insulin infusion (CSII). Despite a lack of evidence that the more expensive treatment with CSII is superior to MDI, both treatments are used widely within the NHS.

The current treatment costs for children and young people with T1D range from £52M to £70M per annum, but this could increase by 50% if all patients used CSII. Previous economic evaluations indicate CSII to be cost-effective in paediatrics, but these were reliant on data from small trials, which were rated as being at risk of bias, and the application of extensive modelling.

Objectives

Internal pilot study

Internal pilot objectives targeted recruitment and generalisability.

Primary objective

- To acquire an understanding of the acceptability of randomisation to MDI or CSII at diagnosis of T1D in children and young people.

Secondary objectives

- To define the characteristics of patients who consent and those who decline to participate.
- To generate data to confirm the standard deviation (SD) used in the sample size calculation of the full study.

Full study

The following objectives were addressed during the first year following the diagnosis of T1D.

Primary objective

- To measure glycaemic control, assessed by glycosylated haemoglobin (HbA_{1c}) concentration 12 months after diagnosis of T1D in participants receiving CSII compared with those receiving MDI.

Secondary objectives

To compare the following outcomes in children and adolescents receiving CSII with those receiving MDI:

- percentage of participants in each group with HbA_{1c} concentrations of < 7.5%
- incidence of severe hypoglycaemia

- incidence of diabetic ketoacidosis (DKA)
- change in height standard deviation score (SDS)
- change in body mass index (BMI) SDS
- insulin requirements (unit/kg/day)
- Pediatric Quality of Life Inventory (PedsQL) score
- cost-effectiveness based on the incremental cost per quality-adjusted life-year (QALY) gained.

Methods

Participants

Participants were recruited from 15 children's diabetes services in England and Wales with experience of treating ≥ 10 patients with CSII. Patients were eligible to participate in the study if they met the following inclusion criteria:

- The patient has newly diagnosed T1D.
- The patient is aged 7 months to 15 years.
- The parent/legal representative of the patient is willing to give consent for the study.
- The parent/legal representative of the patient is able to comply with the treatment regimen and study visits.

Participants with the following characteristics were excluded from the trial:

- previous treatment for T1D
- haemoglobinopathy
- co-existing pathology conditions likely to affect glycaemic control
- psychological or psychiatric disorders
- receipt of medication likely to affect glycaemic control
- allergy to a component of insulin aspart or insulin glargine
- sibling with existing T1D
- known thyroid condition in a non-euthyroid state
- known coeliac disease and inability to maintain a gluten-free diet.

Study procedures

Informed, written consent and, when appropriate, assent was obtained from parents/guardians and patients. Patients were randomised with 1 : 1 web-based block randomisation stratified by centre and age (7 months to < 5 years, 5 years to < 12 years and ≥ 12 years) to treatment with CSII or MDI. Owing to the nature of the interventions, blinding was not possible.

Screening logs were completed at each centre for all newly diagnosed T1D patients. Data were collected on age, sex, ethnicity and deprivation score. The reasons why patients were ineligible, why eligible patients were not approached to participate and why those who were approached declined to participate were recorded along with the dates and times when patients were approached about the SubCutaneous Insulin: Pumps or Injections? (SCIPI) study, when trial information was provided and when consent discussions took place.

The following data, when measured routinely, were collected at baseline:

- biochemical parameters at diagnosis: blood pH, blood glucose, HbA_{1c} concentration and thyroid function tests
- immunology studies: anti-islet cell and anti-glutamic acid decarboxylase antibodies, tissue transglutaminase or other antibody tests for coeliac disease
- growth: height and weight.

Randomised treatment started within 14 days of diagnosis of T1D. Starting insulin doses were calculated according to weight and age, and titrated against blood glucose readings in accordance with local protocols. To support this process, clinical practice guidelines and written patient information were shared from the lead centre for use by recruiting centres at their discretion.

Study visits coincided with clinic appointments at 3, 6, 9 and 12 months. At each visit, the following data were collected:

- HbA_{1c} concentrations
- adverse events
- height and weight
- insulin usage from general practitioner (GP) prescriptions, glucometer and insulin pump downloads (CSII) and patient-kept records (MDI).

The diabetes module of PedsQL was completed at 6 and 12 months.

The primary outcome was HbA_{1c} concentrations at 12 months. The secondary outcomes were (1) HbA_{1c} concentrations of < 48 mmol/mol, (2) severe hypoglycaemia, (3) DKA, (4) T1D- and treatment-related adverse events (AEs), (5) change in BMI and height SDS, (6) insulin requirements, (7) quality of life (QoL) and (8) partial remission rates. The economic outcome was the incremental cost per QALY gained.

Sample size

To achieve 80% power, a sample size of 143 participants in each group was required to detect a difference in means of 0.50, with common SD of 1.50, using a two-group *t*-test with a 0.05 two-sided significance level. An adjustment was made for 10% loss to follow-up, giving a total of 316 participants (158 per group).

Statistical analysis

Primary analysis used the intention-to-treat (ITT) principle. A 0.05 level of statistical significance and 95% confidence intervals (CIs) are used throughout. The statistical analysis plan was developed prior to analysis and is available as a separate document [URL: www.journalslibrary.nihr.ac.uk/programmes/hta/081439/# (accessed 26 July 2018)]. All analyses were conducted using SAS® software (version 9.2; SAS Institute Inc., Cary, NC, USA). SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc. in the USA and other countries. ® indicates USA registration.

When available, HbA_{1c} measurements from samples analysed centrally were used in preference to samples analysed locally. The primary outcome used least squares regression adjusted for age category and centre as a random effect. Binary outcomes are presented as relative risks. A per-protocol analysis was undertaken for the primary outcome to check the robustness of conclusions to major protocol deviations and a safety analysis was conducted on AE data, which included participants in the group to which they had received their insulin at the time of the event.

Economic evaluation

A cost–utility analysis estimated within-trial QALYs based on patients' or their parents' responses to the Health Utilities Index questionnaire, which was administered at 3-monthly intervals. Resource use was measured using questionnaires and by accessing prescription records and electronic patient-linked information costing systems. These included the purchase of pumps or MDI injection devices and associated consumables, cost of insulins and contact with health-care services, including with GPs, with school nurses, as a hospital inpatient, as an outpatient and accident and emergency (A&E) department attendances. National tariff and other standard unit costs were applied to calculate the total costs for the ITT population. A lifetime modelled extrapolation was planned if differences were apparent in HbA_{1c} concentrations between the intervention groups at 12 months. The differences between intervention groups in costs and QALYs were compared, with their joint uncertainty represented in cost-effectiveness acceptability curves.

Results

Recruitment data from the internal pilot study showed acceptable consent rates and no evidence of patient bias, and supported the parameters used in the sample size calculation. The Independent Data and Safety Monitoring Committee recommended that the trial progress to the full study. Data from patients recruited to the internal pilot study were included in the full study.

Participants

In total, 976 patients were diagnosed with T1D and assessed for eligibility in the 15 study centres, of whom 689 were eligible and approached for consent. Of these, 294 (42.7%) consented to participate in the trial; however, one participant withdrew consent for their data to be used immediately following randomisation. Of those patients who declined ($n = 395$), 36 (9%) cited a strong preference for CSII therapy and 259 (66%) cited a strong preference for MDI.

Age, sex and ethnicity did not differ between the group of patients who consented to participate and the group of patients who declined. The median deprivation score for study participants was 17.0 overall (minimum 1.62, maximum 77.23), 27.7 in those who declined owing to a strong preference for CSII (range 3.9–63.9) and 18.0 in those who declined owing to a strong preference for MDI (range 1.2–74.4). A higher score indicates a greater level of deprivation.

In total, 144 patients were randomised to CSII [mean age 9.0 years (SD 4.1 years); 71 (49.3%) female] and 149 patients were randomised to MDI [mean age 9.1 years (SD 4.1 years); 69 (46.3%) female]. Patient characteristics did not differ between treatment arms. All participants received their allocated interventions. One participant who was allocated to CSII and five who were allocated to MDI withdrew from the trial prior to the 12-month follow-up but allowed data collected up to their withdrawal to be used.

Glycosylated haemoglobin levels at 12 months

Intention-to-treat analysis

Data from 97% (CSII, $n = 143$; MDI, $n = 142$) of participants were available. The HbA_{1c} concentrations did not differ between treatment arms: CSII, mean 60.9 mmol/mol (95% CI 58.5 to 63.3 mmol/mol); MDI, mean 58.5 mmol/mol (95% CI 56.1 to 60.9 mmol/mol); and least mean squares-adjusted difference (CSII – MDI), 2.4 mmol/mol (95% CI –0.4 to 5.3 mmol/mol; $p = 0.09$).

Per-protocol analysis

Data from 52.2% (CSII, $n = 87$; MDI, $n = 66$) of participants were included. The HbA_{1c} concentrations did not differ between treatment arms and the direction of results were consistent with those obtained under the ITT analysis population: CSII, 60.2 mmol/mol (95% CI 56.4 to 63.9 mmol/mol); MDI, 59.3 mmol/mol (95% CI 55.3 to 63.3 mmol/mol); and the least mean squares-adjusted difference between treatment groups (CSII – MDI) was 0.9 mmol/mol (95% CI –3.2 to 5.0 mmol/mol; $p = 0.67$).

Percentage of patients with glycosylated haemoglobin levels within the target range 12 months after diagnosis

An ITT analysis was performed on two target values: (1) < 58 mmol/mol, the target set by the National Institute for Health and Care Excellence until August 2015, and (2) < 48 mmol/mol, the new target set in August 2015. Data for 97% (CSII, $n = 143$; MDI, $n = 142$) of participants were available for analysis.

There was no difference between treatment arms for either target. For the target HbA_{1c} value of < 58 mmol/mol: CSII, $n = 66$ (46.2%); MDI, $n = 78$ (54.9%); relative risk (CSII to MDI ratio), 0.84 (95% CI 0.67 to 1.06); and percentage difference (CSII – MDI), –8.8% (95% CI –2.9% to 20.4%). For < 48 mmol/mol: CSII, $n = 22$ (15.4%), MDI, $n = 29$ (20.4%); relative risk (CSII to MDI ratio), 0.75 (95% CI 0.46 to 1.25); and percentage difference (CSII – MDI), –5.0% (95% CI –14.0% to 3.9%).

Related adverse events

Eight episodes of severe hypoglycaemia were reported: six in participants who were treated with CSII and two in participants who were treated with MDI (relative risk 3.1, 95% CI 0.6 to 15.1; $p = 0.17$). Two episodes of DKA occurred in two participants, both of whom were treated with CSII (relative risk 5.2, 95% CI 0.3 to 106.8; $p = 0.24$).

Under the safety analysis population, there were 54 related AEs in 36 participants who were treated with CSII, of which 29 were related to the insulin pump; eight participants had infections at the site of catheter insertion. There were 17 related AEs in 16 participants who were treated with MDI, of which two events were related to injection device; there were no AEs related to injection sites. AEs relating to meter errors, carer errors and incidental illnesses were balanced more evenly across treatment arms.

Change in body mass index and height standard deviation score from diagnosis to 12 months following diagnosis

Data were available for 87% of participants: CSII, $n = 124$; MDI, $n = 132$. There was no significant difference in change in BMI or height SDS between study arms. The mean change in BMI SDS in the CSII group was 0.6 (SD 0.8) and in the MDI group was 0.5 (SD 0.8); the mean difference was 0.1 (95% CI 0.0 to 0.3; $p = 0.13$). The mean change in height SDS was –0.1 (SD 0.5) in the CSII group and 0.0 (SD 0.4) in the MDI group; the mean difference was –0.1 (95% CI –0.2 to 0.0; $p = 0.10$).

Insulin requirements

Data relating to insulin doses were available for 52% of participants (CSII, $n = 87$; MDI, $n = 64$); the least mean squares-adjusted difference for age demonstrated that insulin requirements were higher for participants in the CSII arm than for those in the MDI arm (difference, 0.1 unit/kg/day, 95% CI 0.0 to 0.2 unit/kg/day; $p = 0.01$).

Percentage of participants in each study arm in partial remission

Partial remission was defined as insulin dose-adjusted HbA_{1c} ($IDAA_{1c}$) level of ≤ 9. Data relating to insulin dose and HbA_{1c} concentration at 12 months were available for 51% of participants (CSII, $n = 86$; MDI, $n = 64$). The percentage of participants in partial remission at 12 months was higher in the MDI arm, but the difference was not statistically significant: CSII, 24.4% (21/86 participants); MDI, 32.8% (21/64 participants); and relative risk 0.74 (95% CI 0.45 to 1.24; $p = 0.28$).

Quality of life 12 months after diagnosis of type 1 diabetes

The PedsQL score (diabetes module), as reported by children at 12 months, was available for 71% or participants (CSII, $n = 104$; MDI, $n = 104$), with 26 children in each treatment group being too young to complete the questionnaire. Least mean squares-adjusted difference at 12 months (3.1, 95% CI –0.6 to 6.8) favoured CSII but the result was not statistically significant. Data were available from 86% of parents (CSII, $n = 128$; MDI, $n = 123$). The results for overall QoL favouring CSII, as reported by parents, were statistically significant at 12 months (least mean squares-adjusted difference 4.1, 95% CI 0.6 to 7.6). Parent- and child-reported results are largely consistent and should be considered against a difference of 5 being considered the minimum worthwhile.

Cost-effectiveness of continuous subcutaneous insulin infusion compared with multiple daily injections

Patients randomised to the CSII arm had more than twice as many A&E department visits and inpatient stays relating to the management of T1D than those in the MDI arm. Over the 12-month study period, health-care professionals had a mean of 4.3 (95% CI 0.6 to 8.0) more contacts (texts, e-mails and telephone calls) with patients treated with CSII than with those treated with MDI. The mean total costs were £1863 (95% CI £1620 to £2137) higher for CSII than for MDI, with the majority of this difference being attributable to the additional cost of consumables (£1177) and the device (£520). There were no significant differences in QALYs between the CSII and MDI groups (mean difference –0.006 QALYs, 95% CI –0.031 to 0.018 QALYs). None of the sensitivity analyses affected the base-case result of CSII

being dominated by MDI. The probability of dominance was 69%, with no likelihood of CSII being cost-effective at a threshold of £30,000 per QALY.

Conclusions

Implications for health care

Study participants were recruited from diverse clinical settings, the retention rate exceeded 95% and the characteristics of those recruited to the study did not differ from the background population of patients diagnosed during this time. The findings of the study should therefore be applicable to the population of children treated in the NHS. Treatment with CSII has been embraced widely by the NHS, despite the high treatment cost and paucity of evidence of superior clinical outcomes. Our study shows that, during the first year of treatment, CSII is not associated with better clinical outcomes and is not cost-effective.

Implications for research

The generalisability of our data beyond the first year of diagnosis is uncertain. The observation period should be extended to determine whether or not treatment outcomes diverge over time and how factors, including child development, influence treatment decisions.

Patient advocates and many health-care professionals have a strong belief in the benefits of CSII treatment. In-depth qualitative research is required to learn more about the drivers influencing these preferences and how they alter as children age.

Trial registration

This trial is registered as ISRCTN29255275 and EudraCT 2010-023792-25.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.513

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 08/14/39. The contractual start date was in August 2010. The draft report began editorial review in May 2017 and was accepted for publication in September 2017. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).