Continuous subcutaneous insulin infusion versus multiple daily injection regimens in children and young people at diagnosis of type 1 diabetes: pragmatic randomized controlled trial and economic evaluation

BACKGROUND:

Type 1 diabetes mellitus (T1DM) is a chronic disease with no cure that primarily affects children. Treatment of T1DM consists of insulin injections to help maintain glycemic levels. Poor glycemic control in children can be associated with impaired memory, poor cognitive outcomes, increased risk of depression, and poor growth. Long term uncontrolled glycemic levels can lead to much more serious complications.

OBJECTIVE

The objective of this study was to compare the efficacy, safety, and cost utility of continuous subcutaneous insulin infusion (CSII) with multiple daily injection (MDI) regimens during the first year following diagnosis of T1DM in children and young people.

METHODS

- Pragmatic, multicenter, open label, parallel group, randomized controlled trial and economic evaluation.
- Between May 2011 and January 2016, 976 patients diagnosed with T1DM were assessed for eligibility in 15 study centers in England and Wales. 294 (43%, CSII=144, MDI=149) consented to participate.
- Patients were randomized to treatment with CSII or MDI using 1:1 block randomization stratified by age (7 months to <5 years, 5 years to <12 years, ≥12 years) and by treating center.
- **Inclusion Criteria**
    - Newly diagnosed T1DM
    - Age 7 months – 15 years
    - Parent/legal guardian of the patient are willing to give consent for the study and able to comply with the treatment regimen and study visits.
    - Patients with thyroid disease or celiac disease were eligible if thyroid hormone concentrations or celiac antibodies demonstrated good adherence to treatment
- **Exclusion Criteria**
    - Treated previously for diabetes
    - Hemoglobinopathy
    - Co-existing pathology conditions likely to affect glycemic control
    - Psychological or psychiatric disorders
    - Receipt of medication likely to affect glycemic control
    - Allergy to a component of insulin aspart or insulin glargine
    - Have a sibling with existing T1DM
    - Known thyroid condition in a non euthyroid state
    - Known celiac disease unable to maintain a gluten free diet.
- CSII group - insulin aspart
- MDI group - insulin aspart + insulin glargine or detemir
- Bolus Wizard was used to calculate insulin doses based on blood glucose readings and carbohydrate consumption
- The primary outcome measure was HbA1c 12 months following diagnosis of type 1 diabetes.
- Secondary outcome measures were the percentage of patients in each treatment group with HbA1c within the national target range (6.5%), incidence of severe hypoglycemia and diabetic

ketoacidosis, change in SD of height and body mass index, insulin requirements (units/kg/day), partial remission rate, PedsQL score, and cost utility based on the incremental cost per quality adjusted life year gained.

- Power: 80% with an alpha level of 0.05 to detect a 0.5% difference in HbA1c with a SD of 1.5, 286 patients were required.

RESULTS

Continuous Outcomes	Adjusted Mean (95% CI)		Adjusted mean difference (95% CI)	P
	CSII	MDI		
HbA1c (%) at 12 months*				
Intent-to-treat*	7.7 (7.5 to 7.9)	7.5 (7.3 to 7.7)	2.4 (-2.2 to 2.6)	0.09
Per Protocol*	7.7 (7.3 to 8.0)	7.6 (7.2 to 7.9)	2.2 (-2.4 to 2.6)	0.67
Change in BMI (SD)	0.6 (0.8)	0.5 (0.8)	0.1 (0 to 0.3)	0.13
Change in height (SD)	-0.1 (0.5)	0 (0.4)	-0.1 (-0.2 to 0)	0.10
Insulin requirements (units/kg/day)	0.7 (0.2)	0.6 (0.3)	0.1 (0.0 to 0.2)	0.01

*Primary Outcome

Secondary Binary Outcomes	Total No, No (%) of patients		Relative Risk (95% CI)	P
	CSII (n=144)	MDI (n=149)		
HbA1c<7.5%	143, 66 (46.2)	142, 78 (54.9)	0.84 (0.67 to 1.06)	0.16
HbA1c<6.5%	143, 22 (15.4)	142, 29 (20.4)	0.75 (0.46 to 1.25)	0.28
Incidence of severe hypoglycemia	144, 6 (4.2)	149, 2 (1.3)	3.1 (0.6 to 15.1)	0.17
Incidence of diabetic ketoacidosis	144, 2 (1.4)	149, 0	5.2 (0.3 to 106.8)	0.24
Partial remission (IDAAC <9)	86, 21 (24.4)	64, 21 (32.8)	0.74 (0.45 to 1.24)	0.28

- Mean total costs were higher by $2068 (95% CI $1798 to $2372) for CSII than MDI
- There was no significant difference in QALYs between CSII (0.910) and MDI (0.916; mean difference −0.006, 95% confidence interval −0.031 to 0.018).

STRENGTHS

- High retention rate
- Consistency of age, sex, ethnicity, and deprivation between groups
- Diabetes education was balanced across groups

LIMITATIONS

- No standardization of educational packages or monitoring of treatment protocol
- Possibility of outdated data due to increase in CSII knowledge and experience
- Open label design

CONCLUSION

The results from this study showed that the use of CSII in the first year of type 1 diabetes treatment was not more effective nor cost effective compared to MDI.

Reference:

Blair JC, McKay A, Ridyard C, Thornborough K, Bedson E, Peak M, et al. Continuous subcutaneous insulin infusion versus multiple daily injection regimens in children and young people at diagnosis of type 1 diabetes: pragmatic randomized controlled trial and economic evaluation. *BMJ*. 2019 Apr 3;365:l1226.

Aaron Hanzes, Doctor of Pharmacy Candidate