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UNCERTAINTIES PAGE

What is the best way to deliver subcutaneous insulin to infants, children, and young people with type 1 diabetes mellitus?

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This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the *Cochrane Library*. This paper is based on a research priority identified and commissioned by the National Institute for Health Research's Health Technology Assessment programme on an important clinical uncertainty. To suggest a topic for this series, please email us at uncertainties@bmj.com.

Type 1 diabetes is a common disease of childhood affecting approximately 23 000 children and young people in England.[1] The daily management of type 1 diabetes is burdensome. However, over a lifetime, long term complications are likely to have the greatest adverse impact on quality of life, and pose a significant economic burden to society and the NHS. The prevalence of long term complications is lowest in those with good glycaemic control using intensive insulin regimes in the form of insulin pump therapy or multiple daily injections.[2] A recent review of paediatric diabetes services in the United Kingdom reported that 94% of centres offered intensive insulin regimes, and 78% offer treatment with insulin pump therapy.[3] Despite the widespread availability of insulin pump therapy, data published by the National Diabetes Information Service in 2010 reported that only 1812 people aged less than 18 years were treated with insulin pumps in England.[4]

The National Institute for Health and Clinical Excellence recommends insulin pump therapy as a treatment option from diagnosis of type 1 diabetes for patients aged less than 12 years and for those aged 12 years and above with inadequate glycaemic control on multiple daily injections or disabling hypoglycaemia,[5] with the intention of optimising glycaemic control and quality of life. However, the authors of this guideline recognise that the evidence supporting their recommendations is poor. The additional cost of insulin pump therapy is estimated to be £1700 (€1950; $2770) per annum.[6] At present there is little robust evidence that this additional investment significantly improves glycaemic control, reduces the prevalence of long term complications, or improves quality of life in the paediatric population. We consider the strengths and weaknesses of the key evidence informing national guidelines and clinical practice.

What is the evidence of the uncertainty?

We searched the Cochrane Library, the Health Technology Assessment library, and MEDLINE, using the terms and MeSH headings: diabetes, continuous subcutaneous injection, insulin pump, multiple daily injections, MDI, child, infant, adolescent. A large number of studies were found. These have been critically appraised in two meta-analyses[7 8] and a Health Technology Assessment[6] review.

A Cochrane review[7] reported data from seven paediatric randomised controlled trials collectively studying 210 individuals.[9-15] Studies are summarised in the table⇓. Observation periods ranged from six days to two years. It was estimated that in those treated with insulin pump therapy, HbA_{1c} was 0.2 percentage points lower (95% confidence interval 0.40% to 0.03% (p=0.02)) compared with those treated with multiple daily injections. Differences in study methodology precluded a meta-analysis of hypoglycaemic events.

A recent meta-analysis[8] reported data from six paediatric randomised controlled trials[10 14-18] collectively studying 165 people observed for 4 to 12 months (table⇓). The authors also reported a favourable effect of insulin pump therapy on HbA_{1c} of 0.2 percentage points (95% confidence interval 0.40% to 0.10% (P<0.001)). Insulin dose was significantly lower in patients treated with insulin pump therapy (0.22 units/kg/day, 95% confidence interval 0.31 to 0.14 (P<0.001)). There was no statistically significant difference in the rate of severe hypoglycaemic events or diabetic ketoacidosis.

A meta-analysis of quality of life was not undertaken in either study because of methodological differences between randomised controlled trials. Three studies[9 13 17] used the Diabetes Treatment Satisfaction Questionnaire and all reported greater satisfaction in those treated with insulin pump therapy. The Diabetes Quality of Life Questionnaire for the Young was used in three studies.[9 10 17] There was no difference in outcomes between treatment groups in two studies,[10 17] whereas one group reported greater satisfaction in patients treated with insulin pump therapy but no difference in measures of worry or impact.[9]

Although there is a trend for these meta-analyses to report a favourable effect of insulin pump therapy on glycaemic control, it is difficult to be certain of the importance of this modest reduction in HbA$_{1c}$ on long term clinical outcomes, despite the fact that it is generally accepted that differences in HbA$_{1c}$ of 0.5% or greater are clinically significant.

There are a number of methodological weaknesses in most studies reported to date. Studies recruiting patients with poor glycaemic control and randomising to continued multiple daily injections or a switch to insulin pump therapy may show an improvement with insulin pump therapy, for two reasons:

(1) Selection bias of participants with a preference for insulin pump therapy: patients on established multiple daily injections with good glycaemic control who are satisfied with their current therapy are less likely to be approached or agree to participate in these studies.

(2) Increased contact with diabetes healthcare professionals: at the start of insulin pump therapy patients receive an intensive period of education.

The observation periods in many studies are likely to be too brief for patients to acquire the skills required to use insulin pumps to their full potential,[10 11 14 17] in others too brief to show patient fatigue in the use of this intensive therapy,[9 15 16] and no study has been of sufficient duration to evaluate the impact of insulin pump therapy on long term complications. The number of patients recruited to each study is small, between 16 and 72 per study.

To date, there are only two multicentre studies,[12 13] one two-centre study,[18] and three[9 14 17] of the ten randomised controlled trials are single-centre. Also, to date no randomised controlled study has been delivered in the UK, where healthcare services differ from those in which insulin pump therapy and multiple daily injections have previously been studied. No study has investigated the health economics of insulin pump therapy. Finally, most studies do not use "best possible multiple daily injections" as the comparator to insulin pump therapy. Insulin analogues have been reported to improve glycaemic control in paediatric practice[19] though only one study uses analogue insulin for the treatment of all patients using multiple daily injections.[10]

The Health Technology Assessment review[6] reported evidence from a wider range of sources, including seven randomised controlled trials[9 10 14-18] and 28 observational studies reporting data from 158 patients observed from 7 to 12 months and 1792 patients observed from six months to five years respectively. Representations from patients and industry were also included. The authors concluded that there was a modest reduction in HbA$_{1c}$ in patients treated with insulin pump therapy, but a more important reduction in hypoglycaemic events. The authors reported that improvements in glycaemic control were greater in observational studies than in randomised controlled trials and recognised that these studies are more prone to bias. However, they also commented that observational studies may be more representative of clinical practice. The authors highlighted a number of benefits in quality of life including a reduction in the fear of hypoglycaemia, greater flexibility, and increased ability to cope with unexpected exercise and food.

Is ongoing research likely to provide relevant evidence?

We found only two studies in a search of the World Health Organization's International Clinical Trials Research Platform Portal (Australia New Zealand Trials Registry, clinicaltrials.gov, ISRCTN register) using the terms "children" AND "type 1 diabetes" AND ("pumps" OR "subcutaneous").

ACTRN12610000605099 will recruit 110 young people aged nine to 15.5 years with type 1 diabetes to investigate the effect of insulin pump therapy compared to multiple daily injections of insulin on parental report of behaviour four months after randomisation.

ISRCTN29255275 is led by the authors of this paper. The study will recruit 316 children and young people aged six months to 15 years with newly diagnosed type 1 diabetes to investigate the effect of insulin pump therapy compared to multiple daily injections on glycaemic control, as measured by HbA$_{1c}$, 12 months after diagnosis. Secondary outcomes include measures of quality of life and an economic analysis extrapolated to estimate lifetime costs and benefits.

What should we do in the light of the uncertainty?

To date there are insufficient data to recommend the use of insulin pump therapy rather than multiple daily injections as treatment of first choice to children with type 1 diabetes. Until more robust data are available, treatment with insulin pump therapy should be reserved for those in whom glycaemic control is inadequate, or for those with disabling hypoglycaemia. There is some evidence that quality of life and satisfaction may be improved during insulin pump therapy, but our ability to measure this in routine clinical practice is probably inadequate (although individual and family preference should not be overlooked). Finally, it is important to recognise that the long term benefits of insulin pump therapy are unproven and the benefits and costs of therapy to the individual should be critically appraised on a regular basis.

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Recommendation for further research

Population: infants aged more than 6 months, children, and young people

Intervention and comparison: insulin pump therapy compared with multiple daily injections

Outcome: glycaemic control, frequency of severe hypoglycaemia and diabetic ketoacidosis, quality of life, growth and weight gain, insulin requirements, and cost effectiveness based on the incremental cost per quality of adjusted life years (QALY) gained

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Table

Table 1| Clinical characteristics and between group analyses in patients treated with insulin pump therapy and multiple daily injections studied in randomised controlled trials. Values are mean (standard deviation) unless stated otherwise

Study design	Observation period	Baseline characteristics of patients				Difference in outcomes IPT *v* MDI at study completion
		N	Age (years)	HbA$_{1c}$ (%)	Duration TID (years)	
Crossover RCT[9]	6 months each arm	16	Median 14.2 (range 14.1–17.5)	IPT 8.6 (0.8) MDI 8.5 (1.4)	Not reported	No difference in HbA$_{1c}$ or severe hypoglycaemia. Treatment satisfaction 32.0 (6.5) *v* 21.8 (3.7), P<0.05
Parallel RCT[10]	16 weeks	32	IPT 12.5 (3.2) MDI 13.0 (2.9)	IPT 8.2 (1.1) MDI 8.1 (1.2)	IPT 6.8 (3.8) MDI 5.6 (4.0)	HbA$_{1c}$ (%): 7.2 *v* 8.1, P<0.05. Insulin doses (units/kg/day): 0.9 *v* 1.2, P<0.003. No difference in quality of life
Parallel RCT[11]	6 days	16	IPT 13.3 (4.0) MDI 12.9 (2.4)	IPT 10.5 (2.9) MDI 10.7 (1.1)	Not reported	No significant difference in blood glucose (mean of seven samples/day) or 24 hour glycosuria
Parallel RCT[12]	IPT 10.5 months; MDI 3.5 months; then IPT 7 months	38	IPT 10.0 (3.0) MDI 10.0 (3.7)	IPT 8.3 (0.8) MDI 8.4 (1.1)	IPT 5.6 (3.3) MDI 4.7 (2.9)	No significant difference in quality of life or glycaemic control
Parallel RCT[13]	2 years	72	IPT 11.8 (4.9) MDI 12.3 (4.5)	IPT 8.2 (0.4) MDI 8.4 (0.5)	IPT 12.2 (2.0) MDI 10.4 (1.7) (days)	No difference in HbA$_{1c}$ or severe hypoglycaemia. Insulin doses (units/kg/day): 0.7 *v* 1.1, P=0.001. Treatment satisfaction: 33.1 (0.9) *v* 27.5 (2.0), P<0.001
Crossover RCT[14]	3.5 months each arm	23	Median 11.9 (9.3 to 13.3)	Median 8.9 (6.1 to 10.1)	Median 6.0 (2.5 to 11.0)	No significant difference in HbA$_{1c}$, severe hypoglycaemia, DKA, or quality of life. Treatment satisfaction: 30.6 (3.7) *v* 21.9 (3.8), P<0.001
Parallel RCT[15]	6 months	42	IPT 3.8 (0.8) MDI 3.7 (0.7)	IPT 9.0 (0.6) MDI 9.0 (0.6)	IPT 1.8 (0.6) MDI 1.8 (0.6)	No difference in HbA$_{1c}$ or severe hypoglycaemia
Parallel RCT[16]	24 weeks	26	IPT 3.9 (0.4) MDI 3.8 (0.4)	IPT 7.4 (0.5) MDI 7.6 (0.3)	IPT 1.2 (0.3) MDI 1.6 (0.3)	No difference in HbA$_{1c}$ or severe hypoglycaemia. Fathers of subjects reported greater improvement in quality of life with IPT *v* MDI, P=0.03
Crossover RCT[17]	3.5 months each arm	23	Arm A 11.9 (1.4) Arm B 11.9 (1.5)	Arm A 8.0 (1.1) Arm B 8.3 (0.7)	Arm A 5.3 (1.9) Arm B 6.3 (2.6)	No difference in HbA$_{1c}$, number of hypoglycaemic events. Fasting glucose within target (%): 27 (20) *v* 17 (16), P=0.01. AUC (mg/dL), 24 hr: 377 (377) *v* 638 (727), P=0.04. Hyperglycaemic events, 24 hour: 3.4 (1.2) *v* 2.9 (1.0), P=0.04
Parallel RCT[18]	52 weeks	22	3.6 (1.0)	8.0 (0.8)	1.4 (0.6)	No difference in HbA$_{1c}$, quality of life, episodes of severe hypoglycaemia or DKA

TID: type 1 diabetes; RCT: randomised controlled trial; IPT: insulin pump therapy; MDI: multiple daily injections; DKA: diabetic ketoacidosis; CGM: continuous glucose monitoring; AUC: area under the curve.