

expensive interventions can become affordable if there is strong political will and collaboration with the industry.

The pace of clinical research is accelerating in sub-Saharan Africa. The area needs more international support, but this should be provided without fostering just another form of colonisation.<sup>21</sup> African researchers should have a meaningful say in setting research priorities,<sup>22</sup> and outside support should help develop sustainable local research capacity.

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## Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials

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### Abstract

**Objective** To compare glycaemic control and insulin dosage in people with type 1 diabetes treated by continuous subcutaneous insulin infusion (insulin infusion pump therapy) or optimised insulin injections.

**Design** Meta-analysis of 12 randomised controlled trials.

**Participants** 301 people with type 1 diabetes allocated to insulin infusion and 299 allocated to insulin injections for between 2.5 and 24 months.

**Main outcome measures** Glycaemic control measured by mean blood glucose concentration and percentage of glycated haemoglobin. Total daily insulin dose.

**Results** Mean blood glucose concentration was lower in people receiving continuous subcutaneous insulin infusion compared with those receiving insulin injections (standardised mean difference 0.56, 95% confidence interval 0.35 to 0.77), equivalent to a difference of 1.0 mmol/l. The percentage of glycated haemoglobin was also lower in people receiving

insulin infusion (0.44, 0.20 to 0.69), equivalent to a difference of 0.51%. Blood glucose concentrations were less variable during insulin infusion. This improved control during insulin infusion was achieved with an average reduction of 14% in insulin dose (difference in total daily insulin dose 0.58, 0.34 to 0.83), equivalent to 7.58 units/day.

**Conclusions** Glycaemic control is better during continuous subcutaneous insulin infusion compared with optimised injection therapy, and less insulin is needed to achieve this level of strict control. The difference in control between the two methods is small but should reduce the risk of microvascular complications.

### Introduction

Continuous subcutaneous insulin infusion, often called insulin pump therapy, was introduced in the 1970s as a way of achieving and maintaining strict control of blood glucose concentrations in people with type 1 (insulin dependent) diabetes.<sup>1</sup> Short acting insulin is infused subcutaneously from a portable pump at one



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or more basal rates, with boosts in the dose activated by the patient at mealtimes. With the emergence of new treatment strategies such as insulin “pens,” which encourage multiple injection regimens, and the publication of the diabetes control and complications trial<sup>2</sup> the importance and utility of intensive insulin injection regimens in achieving near normoglycaemia and slowing the development of microvascular complications has become increasingly apparent.

We reviewed the literature on pump therapy and carried out a meta-analysis of glycaemic control and insulin dosage in randomised controlled trials that compared continuous subcutaneous insulin infusion and optimised insulin injection therapy.

## Methods

### Identification and selection of trials

To identify published trials that met the inclusion criteria we searched Medline (1975 to 2000) and Embase (1980-2000) for literature on insulin infusion systems/insulin infusion and the Cochrane database of randomised controlled trials. We also searched a personal (JP) collection of peer reviewed articles and reviews about infusion systems and lists of papers on pump therapy supplied by two manufacturers of insulin infusion pumps (MiniMed and Disetronic). We reviewed cited literature in retrieved articles and information and references supplied by INPUT, a support group for pump patients.

We selected only those studies that were randomised controlled trials of pump therapy compared with optimised insulin injection therapy. We excluded short term studies (two weeks' duration on either

therapy), those in people with newly diagnosed type 1 diabetes, those in pregnant women with diabetes, controlled trials that were not randomised, those that used non-optimised (“conventional”) insulin injection therapy, and those when it was unclear whether injection therapy was optimised. Data were examined independently by two reviewers (JP and MM).

### Outcome measures

We assessed glycaemic control with each method as mean (SD) blood glucose concentration and percentage of glycated haemoglobin. We also noted total daily insulin dose, the type of pump, the type of insulin, and the insulin injection regimen.

### Statistical analysis

We used a random effects model and calculated the weighted mean difference of the standardised blood glucose concentration, percentage of glycated haemoglobin, and insulin dosage on pump and injection therapy (that is, the number of SDs of the value) to compensate for different scales (for example, because of different methods of measuring glycated haemoglobin). We calculated the estimated treatment effects in absolute units by multiplying the combined treatment effects by the average pooled SDs in all studies.

We assessed potential publication bias by a funnel plot and Egger's test.<sup>3</sup> Sensitivity to the estimate of publication bias was assessed by the trim and fill method.<sup>4</sup> We assessed heterogeneity between trials by the  $\chi^2$  test. Sources of heterogeneity were assessed with a random effects regression analysis with age, duration of diabetes and treatment, and year of study as independent variables.

Characteristics of trials included in meta-analysis of continuous subcutaneous insulin infusion versus intensive insulin injections

Author	No of participants	Mean (SD or range) age (years)	Mean (SD or range) duration of diabetes (years)	Duration of treatment (months)	Type of pump	Type of insulin	Injection regimen
Schiffirin, 1982 <sup>8</sup>	16	24.9 (8.8)	10.4 (5.1)	6	Mill Hill	Connaught/Lilly regular	Regular thrice daily; isophane insulin at bedtime
Home, 1982 <sup>6</sup>	10	40.4 (7.3)	23.5 (8.3)	2.5	Mill Hill, Auto-Syringe	Pork Actrapid	Regular thrice daily; ultralente pm
Nathan, 1982 <sup>5</sup>	5	31 (5.7)	7.4 (1.8)	2-3	Auto-Syringe	NA	Regular thrice daily; regular isophane insulin twice daily; ultralente before breakfast
Schiffirin, 1984 <sup>9</sup>	24	13-20	9	4	Mill Hill	Connaught/Lilly regular	Regular thrice daily; isophane insulin pm/bedtime
Dahl-Jørgensen, 1986 <sup>7</sup>	15	26 (19-42)†	12.8†	24	Nordisk	Pork Velosulin	Regular twice daily; isophane insulin am/bedtime
	15	26 (18-32)‡	12.8‡		Auto-Syringe		
Helve, 1987 <sup>10</sup>	65	31.1 (1)	12 (1)	6	Nordisk Auto-Syringe	Velosulin Actrapid	Multiple
Marshall, 1987 <sup>11</sup>	12	36 (21-50)	18 (10-29)	6	Nordisk	Velosulin	Regular twice daily; isophane insulin twice daily/bedtime
Bak, 1987 <sup>12</sup>	20	24 (2)	5.8 (3.8)	6	Graseby	Actrapid	Regular thrice daily; isophane insulin at bedtime
Saubrey, 1988 <sup>13</sup>	21	32 (2.1)	14.5 (1.4)	2.5	Auto-Syringe, Medix	NA	Regular thrice or four times daily; lente bedtime
Schmitz, 1989 <sup>14</sup>	10	36.5 (7.9)	23.7 (2.9)	6	Nordisk	Velosulin	Regular thrice daily; isophane insulin at bedtime
Düsseldorf, 1990 <sup>15</sup>	47†	32 (18-54)	18 (3-44)	24	Nordisk, Promedos	NA	Regular twice, thrice, or four times daily
	49‡				Betatron, Auto-Syringe	NA	Twice daily isophane insulin (or before breakfast injection/bedtime)
Hannaire-Broutin, 2000 <sup>16</sup>	41	43.5 (10.3)	20.0 (11.3)	4	MiniMed, Disetronic	Lispro	Thrice daily monomeric; twice daily isophane insulin (or before breakfast injection/bedtime)

NA=data not available.

\*Regular=regular soluble or short acting insulin.

†Participants on injections.

‡Participants on pump therapy.

## Results

We included 12 randomised controlled trials (table).<sup>5–16</sup> In total 301 participants were randomised to infusion pumps and 299 to optimised injections for between 2.5 and 24 months.

**Blood glucose control**—Glycaemic control was better during pump treatment (figure 1). The standardised mean difference in blood glucose concentrations between insulin pump and optimised insulin injection therapy was 0.56 (95% confidence interval 0.35 to 0.77). There was no significant heterogeneity among trials ( $P=0.17$ ) and no clear publication bias ( $P=0.168$ ). The trim and fill method gave an estimated corrected effect size of 0.39 (0.15 to 0.63). Only duration of treatment was related to effect size in a regression analysis (regression coefficient=0.32, 0.06 to 0.58). This model estimated the effect size as 0.46 (0.14 to 0.77) at six months of treatment and 0.93 (0.30 to 1.57) at two years.

**Glycated haemoglobin**—The percentage of glycated haemoglobin was lower during pump therapy, the standardised mean difference being 0.44 (0.20 to 0.63) (figure 2). This is equivalent to an effect size of 0.51% in original units. There was some evidence of heterogeneity ( $\chi^2 P=0.07$ ), and some possible publication bias ( $P=0.02$ ). The trim and fill method gave an estimated effect size corrected for bias of 0.31 (0.15 to 0.48). None of the measured variables was significantly related to effect size in regression analysis.

**Insulin dose**—The improved control during insulin pump therapy was achieved at a reduced total daily insulin dosage. The standardised mean difference in insulin dose was 0.58 (0.34 to 0.83). This represents a mean dosage reduction of 14% during pump therapy. The effect size was 7.58 units/day in original units. There was some evidence of heterogeneity ( $P=0.07$ ). The funnel plot showed some bias, though the result of Egger's test was not significant ( $P=0.17$ ). The effect size corrected for bias was 0.42 (0.25 to 0.58). In regression analysis the duration of treatment was negatively related to effect size (regression coefficient=-0.41, -0.66 to -0.15). The model estimated the effect size to be 0.66 (0.33 to 0.10) at six months and 0.05 (-0.59 to 0.70) at two years of treatment.

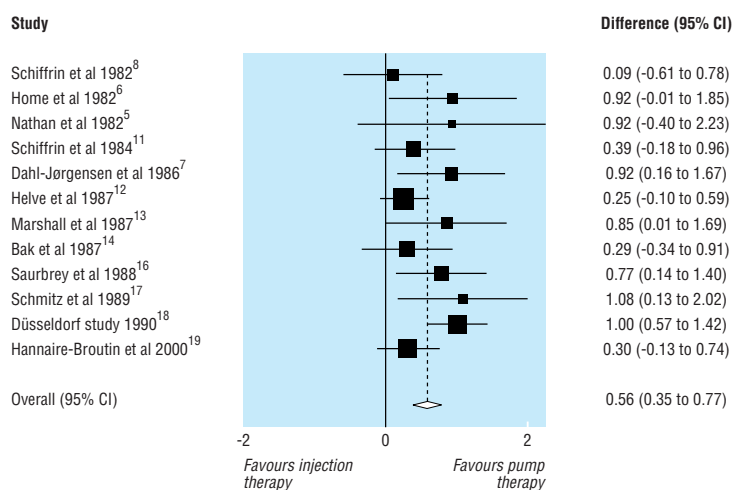
**Variability in blood glucose concentration**—Using SD of blood glucose concentration as a measure of glycaemic variability, we found the variability was significantly higher with insulin injections than with pump therapy (weighted geometric mean of the SD ratios 1.27, 1.11 to 1.47).

## Discussion

Meta-analysis of 12 randomised controlled trials shows that use of insulin pumps results in better glycaemic control than optimised insulin injection therapy but that the difference is relatively small—about 1 mmol/l for blood glucose concentration and 0.5% for percentage of glycated haemoglobin.

### Potential influences on glycaemic control

Glycaemic control during optimised injection therapy may be affected by the regimen used and the intensity of its application. There were many different injection regimens used in the trials reported here, and we cannot make judgments about their appropriateness.

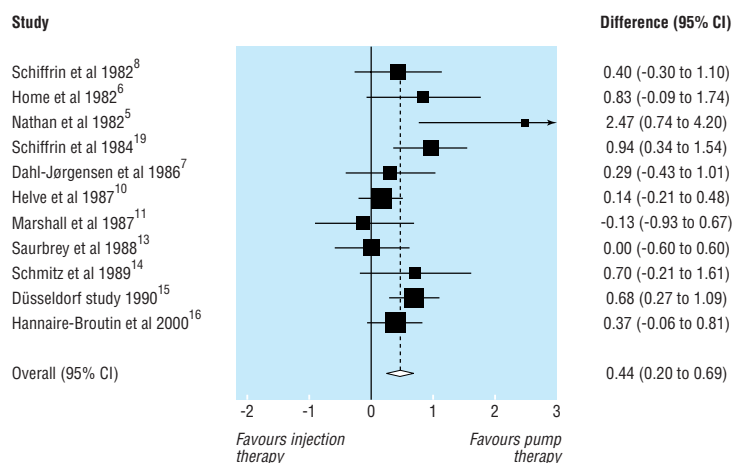


**Fig 1** Standardised mean differences (95% confidence interval) in blood glucose concentration achieved during insulin pump compared with optimised insulin injection therapy

Though this introduces some uncertainty into the conclusions, the results were surprisingly consistent across trials. The only identified source of heterogeneity was a tendency for trials with a longer duration to be associated with a larger difference in control of glycaemia between pump and injection therapy and a smaller difference in insulin dosage. This finding is consistent with the known effect of pump therapy in improving insulin sensitivity and reducing insulin resistance in people with type 1 diabetes.<sup>17 18</sup>

### Clinical significance of improved control

What is the clinical significance of the small difference between the strict glycaemic control of pump and optimised injection therapy? The risk of development and progression of microvascular complications extends over the entire range of glycated haemoglobin values and there is no threshold (short of normoglycaemia) below which there is no risk.<sup>19</sup> The standardised mean difference for glycated haemoglobin of 0.44 in this meta-analysis corresponds to a reduction in HbA<sub>1c</sub> of about 0.5% in the diabetes control and complications trial (where the SD for HbA<sub>1c</sub> in the intensively



**Fig 2** Standardised mean differences (95% confidence interval) in percentage of glycated haemoglobin during insulin pump compared with optimised insulin injection therapy

### What is already known on this topic

Continuous subcutaneous insulin infusion (insulin pump therapy) produces good long term control of blood glucose concentrations in people with type 1 diabetes

Control of blood glucose concentration is substantially better on pump therapy than conventional (non-optimised) injection therapy

It is unclear how glycaemic control on pump therapy compares with modern optimised insulin injection regimens

### What this study adds

Though glycaemic control was better during continuous subcutaneous insulin infusion than optimised insulin injection therapy, the difference was relatively small

Continuous subcutaneous insulin infusion is an effective form of intensive insulin therapy that should lower the risk of microvascular complications

Insulin pump therapy is unnecessary for most people with type 1 diabetes and should be reserved for those with special problems with optimised insulin injections

managed group was 1.1-1.3%). This degree of improvement in control was associated with a reduction in risk of retinopathy of about 25%. In people with intensively controlled glycaemia the absolute risk reduction for sustained progression in retinopathy associated with a difference in HbA<sub>1c</sub> of 0.5% was about 0.5 cases per 100 patient years. Thus, maintaining this difference in control between insulin pump and injection therapy for 10 years would reduce the number of patients developing retinopathy of this degree by about 5%. The cost effectiveness of insulin pump versus insulin injections for this degree of benefit will need to be assessed.

#### Hypoglycaemia and variability of glycaemic control

A weakness of our study is that because of poor reporting and short duration of studies we could not assess the relative frequencies of potential side effects, particularly severe hypoglycaemia, ketoacidosis, and weight gain. For hypoglycaemia, for example, many studies were too short in duration to have more than one episode of severe hypoglycaemic reported on either treatment.<sup>5 6 8 9 13 14</sup> However, we found that oscillations in blood glucose concentration were also significantly less during pump treatment. This may contribute to the lower frequency of hypoglycaemia reported in other studies<sup>20-23</sup> and is probably related to the lower variability in subcutaneous insulin absorption during pump infusion compared with injection treatment.<sup>24</sup>

#### Conclusions and recommendations

We conclude that continuous subcutaneous insulin infusion is an effective form of intensive insulin therapy for people with type 1 diabetes as glycaemic control is slightly but significantly better than during optimised insulin injections. However we consider that in general insulin pump should be reserved for those with special problems such as unpredictable hypoglycaemia or a marked increase in blood glucose concentration at

dawn, despite best attempts to improve control with optimised injection regimens.<sup>25 26</sup>

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