Papers

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.[1] Short acting insulin is infused subcutaneously from a portable pump at one or more basal rates, with boosts in the dose activated by the patient at mealtimes. Overall control, as measured by mean blood glucose concentrations and percentage of glycated haemoglobin, is considerably improved during treatment with insulin infusion pumps compared with the non-optimised insulin injection therapy that was prevalent in management of diabetes until relatively recently.[2 3] However, 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[4] the importance and utility of intensive insulin injection regimens in achieving near normoglycaemia and slowing the development of microvascular complications has become increasingly apparent.

Though there have been several randomised controlled trials of insulin pumps compared with optimised insulin injection regimens, many had relatively small numbers of participants.[5-8] Some of these studies showed better control with pumps,[5 6] and others showed broadly similar control.[7 8]

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

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BMJ 2002;324:1–6

with optimised insulin injection therapy. We considered optimised injection therapy as part of the trial design if multiple insulin injections were used, there was adjustment of insulin dosages or timing, or both, according to hospital and home monitored blood glucose concentrations, or the authors described the regimen as "intensive" or "optimised." We did not included trials of alternative infusion and injection systems, such as the "pen infuser" and jet injectors, which are not based on electromechanical pumps or regular subcutaneous needle injection. We also 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. When several publications reported different aspects of the same study—for example, effect on glycaemic control in one paper and subsequently effects on various microvascular complications in another paper—we chose only one paper to represent the trial data on glycaemic control.

We extracted data from text, tables, and graphs. Data were examined independently by two reviewers (JP and MM). Differences over inclusion of studies and interpretation of data were resolved by consensus reached after discussion.

Outcome measures

We assessed glycaemic control with each method as mean (SD) blood glucose concentration (to include whole blood, plasma, and serum glucose concentration) and percentage of glycated haemoglobin (to include HbA_{1c}, HbA_1 and glycated haemoglobin measurements made by different methods). We also noted total daily insulin dose on the two regimens. We recorded the type of pump, the type of insulin, and the insulin injection regimen.

Statistical analysis

We used a random effects model (StataCorp, College Station, TX, USA) for the meta-analysis. We 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.[9] Sensitivity to the estimate of publication bias was assessed by the trim and fill method.[10] We assessed heterogeneity between trials by the χ^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. We tested the robustness of the analyses in sensitivity analyses by comparing the summary results of random effects meta-analysis with meta-analysis using a fixed effect model and analysis with data in absolute rather than standardised units.

We tested the hypothesis that variability in blood glucose concentration was less during continuous insulin infusion than during injection therapy by calculating the ratio of the minimum variance

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
Schiffrin, 1982[8]	16	24.9 (8.8)	10.4 (5.1)	6	Mill Hill	Connaught/Lilly regular	Regular thrice daily; isophane insulin at bedtime
Home, 1982[6]	10	40.4 (7.3)	23.5 (8.3)	2.5	Mill Hill, Auto-Syringe	Pork Actrapid	Regular thrice daily; ultralente pm
Nathan, 1982[5]	5	31 (5.7)	7.4 (1.8)	2-3	Auto-Syringe	NA	Regular thrice daily; regular isophane insulin twice daily; ultralente before breakfast
Schiffrin, 1984[11]	24	13-20	9	4	Mill Hill	Connaught/Lilly regular	Regular thrice daily; isophane insulin pm/bedtime
Dahl-Jørgensen, 1986[7]	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[12]	65	31.1 (1)	12 (1)	6	Nordisk Auto-Syringe	Velosulin Actrapid	Multiple
Marshall, 1987[13]	12	36 (21-50)	18 (10-29)	6	Nordisk	Velosulin	Regular twice daily; isophane insulin twice daily/bedtime
Bak, 1987[14]	20	24 (2)	5.8 (3.8)	6	Graseby	Actrapid	Regular thrice daily; isophane insulin at bedtime
Saurbrey, 1988[16]	21	32 (2.1)	14.5 (1.4)	2.5	Auto-Syringe, Medix	NA	Regular thrice or four times daily; lente bedtime
Schmitz, 1989[17]	10	36.5 (7.9)	23.7 (2.9)	6	Nordisk	Velosulin	Regular thrice daily; isophane insulin at bedtime
Düsseldorf, 1990[18]	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[19]	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.

weighted geometric means of the SDs of blood glucose concentrations on the two regimens.

Results

We identified 13 randomised controlled trials that compared glycaemic control on continuous subcutaneous insulin infusion compared with optimised insulin injections.[5–8 11–19] In one report the error terms were ambiguous. As we could not reach consensus about reliable extraction of data we omitted this trial from the analysis.[15] The table shows the characteristics of the analysed trials. Eleven trials were of crossover design.[5 6 8 11–14 16–19] Nine different infusion pumps were used. In total 301 participants were randomised to infusion pumps and 299 to optimised injections for between 2.5 and 24 months. This represented 2522 patient months of pump treatment.

Blood glucose control

Figure 1 shows that glycaemic control was better during pump treatment. 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). The estimate from the fixed effects model was similar (0.53, 0.36 to 0.70). The treatment effect in terms of absolute units was 1.06 mmol/l (0.88, 0.52 to 1.24 mmol/l with unstandardised data).

The results of the χ^2 tests showed no significant heterogeneity among trials (P=0.17). There was no clear publication bias in a funnel plot, and the result of Egger's test was not significant (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

Figure 2 shows that the percentage of glycated haemoglobin was lower during pump therapy, the standardised mean difference being 0.44 (0.20 to 0.63). This is equivalent to an effect size of 0.51% in original units, consistent with that seen in a meta-analysis with unstandardised data (0.45%, 0.20% to 0.71%). The fixed effect model gave a similar standardised mean difference to the random model (0.41, 0.23 to 0.58). There was some evidence of heterogeneity (χ^2 P=0.07), and a funnel plot and Egger's test (P=0.02) revealed some possible publication bias. 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

Figure 3 shows that 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, which was similar to that seen in a meta-analysis with unstandardised data (7.33, 4.07 to 10.59 units/day).

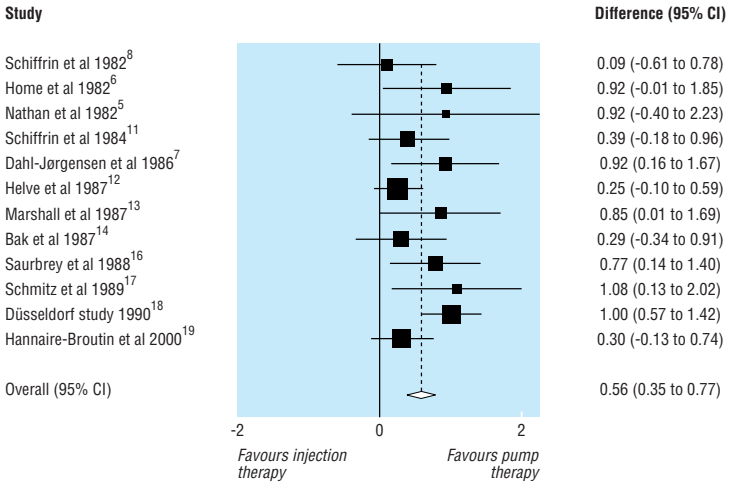

Fig 1 Standardised mean differences (95% confidence interval) in blood glucose concentration achieved during insulin pump compared with optimised insulin injection therapy

The estimate from the fixed effect model was similar to that of the random effects model (0.53, 0.36 to 0.71).

Analysis of insulin dose showed 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

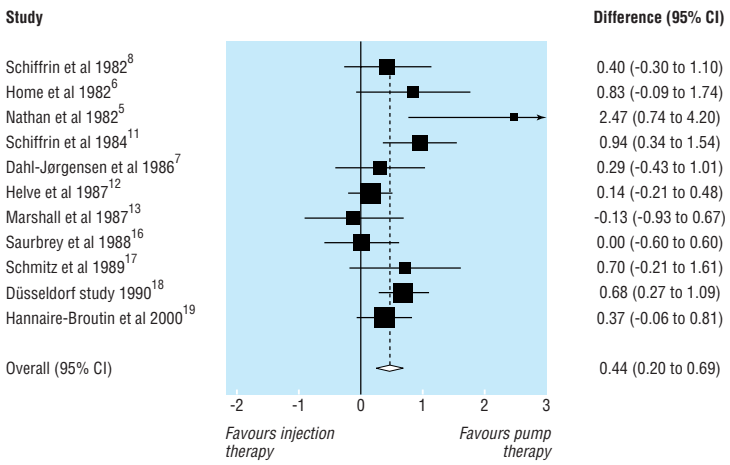

Fig 2 Standardised mean differences (95% confidence interval) in percentage of glycated haemoglobin during insulin pump compared with optimised insulin injection therapy

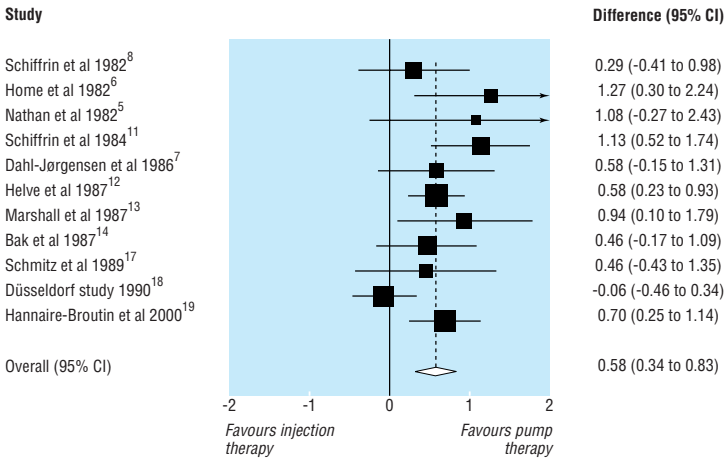

Fig 3 Standardised mean differences (95% confidence interval) in total daily insulin dose during insulin pump compared with optimised insulin injection therapy

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. The main inclusion criterion in the studies was that patients should agree to and be capable of using the pump and its associated procedures. As this is the prerequisite of pump therapy in clinical practice[20] the results of our meta-analysis are applicable to the general population of people with type 1 diabetes, though few of the participants in these studies had severe complications such as clinical nephropathy (with persistent proteinuria shown by positive result on dipstick testing).

Potential influences on glycaemic control

Our results of meta-analysis were not modified by the publication date of the trials, though there are several potential reasons why insulin pump therapy in the early 1980s might have been less effective than modern practice. Early pumps had few or no alarm features for events such as low battery or occlusion of delivery and no facility for automatic change in basal rate of infusion. The type of insulin used in the pump might also be important as unbuffered short acting insulin, used particularly in North America in the first years after the introduction of insulin pumps, was more likely than buffered insulins to occlude the delivery cannula and disrupt control.[21 22] The most recent trial in this survey used the monomeric insulin analogue, lispro, in the pump.[19] This is now considered to be the pump insulin of choice,[23–26] but the results of the one lispro pump study in this meta-analysis were broadly consistent with the overall result of our analysis (standardised mean differences with lispro were 0.30 (−0.13 to 0.74) for blood glucose concentration and 0.37 (−0.06 to 0.81) for glycated haemoglobin, favouring pump treatment[19]).

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. 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.[27 28]

We excluded from our analysis the few trials in patients with newly diagnosed type 1 diabetes[29] because the likely remaining endogenous β cell function would favour good control in any type of insulin therapy[30] and obscure differences between pump and injection treatment. We also did not analyse trials in pregnant women because the number of studies is small[31–33] and because we considered them to be a special group of patients, with changing control throughout pregnancy and a high level of motivation generally unrepresentative of most people with type 1 diabetes.

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? Analysis of the results of the diabetes control and complications trial[34] has shown that 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. The standardised mean difference for glycated haemoglobin of 0.44 in this meta-analysis corresponds to a reduction in HbA_{1c} of about 0.5% in the diabetes control and complications trial (where the SD for HbA_{1c} in the intensively 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%. However, the relation between the absolute risk (hazard rate per 100 patient years of treatment) and HbA_{1c} was curvilinear, with a smaller rate at a lower than at a higher HbA_{1c}. In people with intensively controlled glycaemia the absolute risk reduction for sustained progression in retinopathy (three steps on the early treatment of diabetic retinopathy scale) associated with a difference in HbA_{1c} 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.[5 6 8 11 16 17] However, as well as the lower mean blood glucose concentration, we found that oscillations in blood glucose concentration, as measured by SD, were also significantly less during pump treatment. This may contribute to the lower frequency of hypoglycaemia reported in other studies[35–38] and is probably related to the lower variability in

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

subcutaneous insulin absorption during pump infusion compared with injection treatment.[39]

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.[20 40]

Contributors: JP initiated the study, analysed the data, wrote the first draft of the paper, and is guarantor. MM analysed the data. SK performed the statistical analyses. All authors collaborated on the final version of the paper.

Funding: None.

Competing interests: King's College London has received financial support for some studies on continuous subcutaneous insulin infusion from MiniMed, a manufacturer of insulin pumps.

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(Accepted 5 November 2001)