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Optimization of basal insulin delivery in Type 1 diabetes: a retrospective study on the use of continuous subcutaneous insulin infusion and insulin glargine

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Abstract

Aims To compare the effects on glycaemic control after using continuous subcutaneous insulin infusion (CSII) or insulin glargine.

Methods Data were obtained from 17 diabetes outpatient clinics in Sweden, employing the same diabetes data management system. Type 1 diabetic patients using multiple dose injections were included prior to starting on either CSII (n = 563) or glargine (n = 513). The median duration of therapy was 25 months for CSII and 6 months for glargine. The comparison between the treatment modalities was carried out by multiple regression analysis and logistic regression analysis in an attempt at reducing the influence of confounding factors.

Results The mean HbA_{1c} decrease was 0.59 ± 1.19% for CSII and 0.20 ± 1.07% for glargine ($P < 0.001$, when assessed by logistic regression). An additional 0.1% lower HbA_{1c} would be expected if glargine had been optimized with basal insulin 40–60% of the daily dose. The more pronounced effect of CSII was achieved with a lower daily dosage of insulin. In a multiple regression analysis with a change of HbA_{1c} as the dependent variable, the following variables were significant: choice of treatment ($P < 0.001$), HbA_{1c} prior to treatment ($P < 0.001$) and BMI prior to treatment ($P < 0.01$).

Conclusion Both regimes improved metabolic control, but CSII resulted in significantly higher reduction in HbA_{1c} than after insulin glargine treatment, particularly in those individuals who had higher levels of HbA_{1c} at baseline.

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Keywords basal insulin delivery, Type 1 diabetes, continuous subcutaneous insulin infusion, insulin glargine, optimization

Introduction

The long-acting basal insulin analogue glargine, combined with multiple daily insulin injections (MDI), has been found to be more effective than the intermediate-acting NPH with MDI [1]. Furthermore, continuous subcutaneous insulin infusion (CSII) is found to be superior to NPH with MDI in Type 1 diabetes [2]. Because the pharmacokinetics of glargine mimics CSII [3], glargine might be expected to have comparable metabolic control as CSII [1,4]. To date there have been few randomized studies comparing these treatments, and those that are available include a small numbers. Leopore *et al.* [1] have reported no differences in glycaemic control between CSII and glargine.

To achieve the statistical power required to compare therapies we have used retrospective data from a diabetes management system. There exists a certain selection bias when comparing CSII with glargine with retrospective data. For example, the proportion of basal insulin might be optimal in the use of CSII, but this would not be the case for the new and less well-known drug glargine. The baseline HbA_{1c} level and

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other variables might also differ and be a risk of bias. This may be partly overcome and managed if foreseeable critical factors are recognized, analysed with appropriate methods, and taken into consideration when interpreting the results.

Design and methods

The diabetes management system

We used data from a medical record system (Journalia AB, Sweden), which allows tracking activities, evaluating therapies, and calculating risks from large data bases [5]. It includes a comprehensive diabetes management module (Diab-Base). Specialist physicians and nurses use this system daily. The medical records and prescriptions, as well as instructive letters with individualized targets for the patients, are compiled from coded phrases combined with additional codes and free text. National guidelines for the treatment of diabetes have influenced the development of the system. In addition there are educational reminders supporting the daily work, including suggestions as to how insulin doses can be balanced. Diab-Base is currently used in one fifth of all adult outpatient diabetes clinics in Sweden. Reports and benchmarking are being generated annually from these centres as well as being included in the national evaluation of diabetes care in Sweden [6]. With this kind of feedback the process of diabetes care is getting more standardized and predictable.

Subjects and therapy

This study, as approved by the Ethics Committee of Göteborg University, comprised data obtained from 17 outpatient diabetes clinics with professional diabetes teams using Diab-Base. Data for the study were imported via the Internet in 2003 relating to 13 619 individuals who made in total 168 230 visits. Included in the comparison were adult patients with Type 1 diabetes currently treated. They were monitored regularly in the management system, and used MDI before being introduced to CSII (n = 563) or MDI with insulin glargine (n = 513) (Table 1). The earliest data obtained in the CSII group was from 1996 and from 2000 in the glargine group. The mean time for the last visit was in April 2003 for both groups. The median duration of therapy with CSII was 25 months (interquartile range 14–38) and with glargine 7 months (interquartile range 5–12). The median duration of diabetes was 20 years (interquartile range 12–29) in the CSII group and 22 years (interquartile range 13–31) in the glargine group. At the time of the study, insulin pumps as well as glargine were used in 10% of insulin treated individuals. The cost for CSII treatment is reimbursed in Sweden. Patients were generally selected for the therapies due to persistently high HbA_{1c} or unstable blood glucose values, despite prolonged efforts to improve glycaemia. The value of HbA_{1c} before the introduction to CSII or glargine was significantly lower in patients taking glargine. This detail and some other clinical features before starting CSII or MDI with glargine are shown in Table 1. Both groups used similar insulin regimes with MDI before being introduced to CSII or glargine. Prior to change of therapy lispro or aspart together with NPH were the most common. Microalbuminuria at start, defined as > 20 mg/l or > 20 μg/min, was more common among CSII-users. The glargine group showed more signs of neuropathy before starting treatment, by clinical examination, reflexes, the tuning fork, or monofilament. The frequency of laser treatment for diabetic eye disease and of smoking, was similar in both groups at baseline. The basic education in MDI was the same for both groups, however, the use of the pump is an additional educational tool. Initially, the visits of patients starting on CSII were more frequent, but there was no difference in the time interval between visits (CSII 3.53 ± 2.1 months vs. glargine 3.58 ± 2.2) after 6 months. The HbA_{1c} values after treatment change was included in the analyses if at least 30 days had passed. The methods used to measure HbA_{1c} have been calibrated to coincide with the standard Swedish high performance liquid chromatography Mono-S method [6]. The HbA_{1c} values determined using this technique, are approximately 1.2% lower than the DCCT standard.

Table 1 Clinical features of patients before starting on CSII or MDI with glargine

Variable	CSII	Glargine	P-value
Number ((n)	563	513	
Age (years)	40.8 ± 12.0	42.7 ± 13.2	< 0.001
Women (%)	56	50	n.s.
BMI (kg/m^2)	25.0 ± 3.4	24.7 ± 3.5	n.s.
Insulin (U/kg/day)	0.63 ± 0.27	0.63 ± 0.25	n.s.
Insulin injections (n/day)	4.0 ± 0.8	4.2 ± 0.9	< 0.05
Basal insulin (%)	44.4 ± 19	43.0 ± 15	n.s.
HbA_{1c} (%)	7.64 ± 1.5	7.42 ± 1.6	< 0.05
Laser treatment (%)	14.9	15.4	n.s.
Microalbuminuria (%)	21	16	< 0.05
Neuropathy (%)	14	19	< 0.05
Smoking (%)	11	13	n.s.

Statistical analysis

Variables are presented as mean ± SD. The main outcome measure was the change of HbA_{1c} during treatment. For comparisons of baseline variables Student's t-test and Fisher's exact test were applied.

To study the influence on metabolic control of other factors, multiple linear regression analyses were performed with change of HbA_{1c} (last HbA_{1c}-HbA_{1c} prior to treatment) as a dependent variable (Y). The multiple regression analysis included the zero-one variable for choice of treatment. This imposes a potential problem in relation to the non-normal distribution when determining the corresponding P-value. This was addressed by using logistic regression analysis with the zero-one variable as the dependent one and change of HbA_{1c}, HbA_{1c} prior to treatment, BMI and time period since start of treatment as independent variables. Within treatment groups HbA_{1c} prior and after treatment were compared by paired T-test. All P-values were two-tailed.

Results

The CSII group started with higher HbA_{1c} values than the glargine group (Table 1). Decrease of HbA_{1c} at different HbA_{1c}

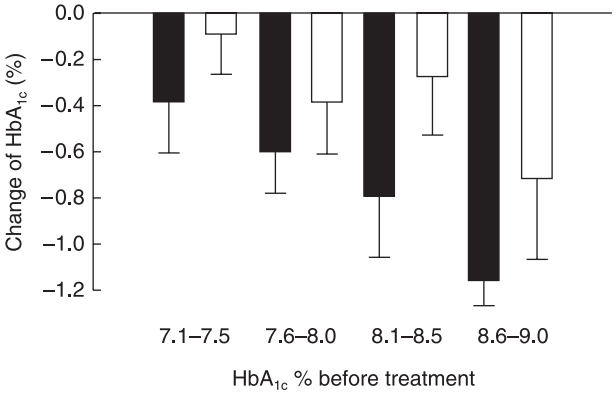

Figure 1 Magnitude of change in HbA_{1c} (mean with 95% CI) after glargine (□) vs. CSII (■), relative to pretreatment levels of HbA_{1c}.

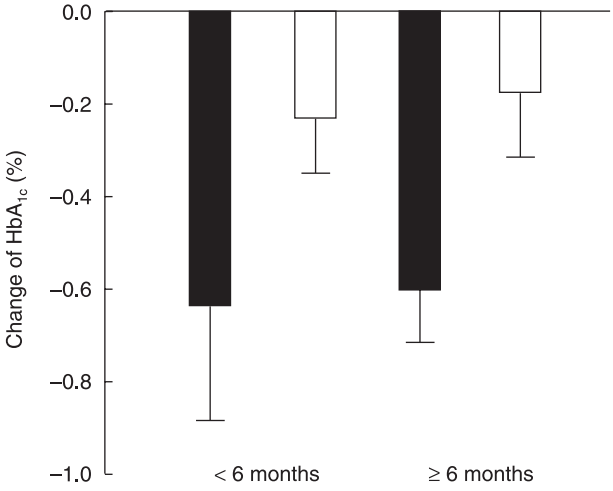

Figure 2 Influence of duration of treatment with CSII (■) or glargine (□) on the change in HbA_{1c} (mean with 95% CI).

levels prior to treatment with CSII, or glargine, are shown in Fig. 1. In both treatment groups significant reductions in HbA_{1c} were noted ($P < 0.001$). The most substantial decrease occurred in patients with high initial HbA_{1c} values. With CSII the mean decrease was 0.59 ± 1.19% and with glargine 0.20 ± 1.07% ($P < 0.001$, when assessed by logistic regression). The number of meal doses was 3.5 ± 0.9 and the number of basal rate settings was 3.0 ± 2.1 with CSII. Insulins used in pumps were: aspart (13%), lispro (74%) or regular (13%). Meal insulins used combined with glargine were: aspart (30%), lispro (63%) or (C) regular (7%). The number of injections per day was 4.2 ± 0.8 with glargine. Insulin glargine was taken: once daily before breakfast (15%), lunch (5%), dinner (7%), or at bedtime (73%). The basal insulin percentage of total insulin dose was higher with CSII, 54.3 ± 14% vs. 45.0 ± 10% for glargine ($P < 0.001$). A more pronounced effect of CSII was achieved with a lower daily dosage of insulin ($P < 0.001$) after CSII (0.57 ± 0.25 U/kg/day) than after glargine (0.62 ± 0.19 U/kg/day). Compared to baseline (Table 1) the mean daily dose was lowered by 9,5% after CSII ($P < 0.001$) and by 1.6% after glargine ($P < 0.05$).

Figure 2 shows the relation between duration of therapy and change of HbA_{1c}. When analysed by multiple regression analysis, the difference in the duration of therapy showed no relation to a decrease in HbA_{1c}. We developed a model to predict a change of HbA_{1c} based on type of treatment, namely HbA_{1c} prior to treatment and BMI prior to start (Table 2). The following independent variables were significant: the type of treatment ($P < 0.001$), HbA_{1c} prior to treatment ($P < 0.001$) and BMI prior to treatment ($P < 0.001$). The following variables were found to be not significant and thus omitted from the model: duration of therapy, age, sex, number of daily injections before start, percentage of basal insulin before the start, the duration of diabetes, the number of profiles, and the units of insulin/kg/day.

To study the role of the proportion of basal insulin we analysed data from two subgroups of patients receiving glargine. Subgroup A included those with a basal proportion of insulin in the interval 40% to 60% ($n = 302$) and subgroup B included those outside that interval ($n = 211$). In subgroup A the mean percentage of basal insulin was 48.4 ± 5% compared to 47.9 ± 10% before start (n.s.). Insulin dose decreased from 0.64 ± 0.25 to 0.62 ± 0.18 U/kg/day ($P < 0.05$). The level of HbA_{1c} decreased 0.31%, from 7.49 ± 1.5% to 7.18 ± 1.2% ($P < 0.001$). An additional 0.1% lower HbA_{1c} was thus to be expected if the proportion of glargine had been optimized to 40–60%. In subgroup B there was no significant change of mean HbA_{1c} (from 7.24 ± 1.7% to 7.17 ± 1.6%) and no significant change of mean insulin dose (from 0.62 ± 0.3 U/kg/day to 0.61 ± 0.2 U/kg/day). Regression analyses were performed for comparisons. The same model, as presented above, was used for the main groups. Subgroup A was found to have a more pronounced effect than subgroup B ($P < 0.05$) and appeared less effective than CSII ($P < 0.01$).

Table 2 Multiple regression model with change of HbA_{1c} as response variable and type of treatment (CSII or glargine), HbA_{1c} before start and BMI before start as independent variables from all patients in the study

Variable	Coefficient Beta	Standard error	*P*-value
Intercept	2.19	0.23	< 0.001
X_1 = Treatment (CSII = 1, Glargine = 0)	−0.25	0.06	< 0.001
X_2 = HbA_{1c} percentage before start	−0.40	0.02	< 0.001
X_3 = BMI before start	0.02	0.01	< 0.01

Discussion

Information on the effectiveness of therapy in everyday practice might be obtained from medical record systems. This is often difficult to achieve due to deficiencies in coding and in the architecture of the systems used [7]. Coded information from prescriptions, laboratory data, and text relating to clinical findings need to be compiled and combined with free text

to create readable records as well as followed up for statistical analyses. There are also certain constraints due to design and risk of bias. For this reason we did not use data about hypoglycaemia. Other studies on CSII [8] as well as on glargine [9] have shown less hypoglycaemic problems during night in particular, and overall risks of hypoglycaemia do not appear to be higher. To investigate bias it is necessary to use several statistical techniques. In our study we included multiple regression and logistic regression analysis to reduce the influence of confounding factors. A cautious interpretation of the results is also necessary. The data should then be used to attempt to confirm earlier results demonstrated in strictly controlled experimental studies. The data may also be used to generate hypotheses and plan prospective studies.

In several studies involving glargine it has been difficult to detect a significant difference in HbA_{1c} between treatment groups. In a recent review only three of 14 trials on glargine were of an adequate size to achieve 90% statistical power to detect a mean 0.5% difference in HbA_{1c} [9]. In smaller studies, continuous glucose monitoring system (CGMS) may be more useful than HbA_{1c} as the total daily glycaemia is an important determinant of metabolic control [10]. King and Armstrong [11] used this method in 19 patients, and suggested that therapy with CSII mimics physiology more effectively in creating more stable blood glucose profiles, compared with MDI with insulin glargine. In the present study including 1076 patients there was enough statistical power to detect a better metabolic control in CSII users than in those using MDI with insulin glargine. In cases with high levels of HbA_{1c} prior to change of treatment the difference in HbA_{1c} between the groups was more pronounced, approximately 0.5%.

Patients on CSII in the present study had significantly higher HbA_{1c} than those on glargine. This circumstance could easily lead to erroneous interpretations as the higher the HbA_{1c} values recorded, the greater the fall of HbA_{1c} in the treatment. Including them in the multiple regression and the logistic regression analyses, however, eliminated the influence of the baseline values. There are other possibilities of bias that cannot easily be removed by statistical methods as we lack the necessary measurements or knowledge. Patients on CSII might cooperate more with treatment due to better education, or to the presence of threatening problems like microalbuminuria. We belive that the continuous infusion appeared to be the dominating factor favouring pump treatment. This degree of improvement in HbA_{1c} may affect both the development of diabetic complications, and the economics of health care expenditure for diabetes [12,13].

The variable basal insulin delivery preprogramming in CSII treatment may help to achieve better insulin coverage diurnally [4,11]. However, we could not demonstrate that the number of such basal insulin profiles during pump therapy led to improved HbA_{1c}. More prospective studies are needed. Dividing the dose of glargine and giving it twice daily might stabilize insulin action by reducing the variability in subcutaneous insulin absorption or prolonged insulin action [14,15].

Glargine has been used for a shorter period than CSII. In Sweden glargine became available from the year 2002. A consequence of the relative lack of experience might lead to inappropriate proportions of basal insulin. In subgroup analyses we found that glargine could be more effective, although not as efficient as CSII, if the percentage of basal insulin was kept within 40–60%.

Duration of treatment showed no significance in the multiple linear regression analysis with change of HbA_{1c} as the dependent variable. A likely interpretation to this finding is that the fall of HbA_{1c} occurs early within a few months. Concomitantly with improved control there is often a need to decrease the daily insulin dose. A lowered daily insulin dose during CSII-therapy has earlier been reported in comparison with NPH [8] and has also been noted after glargine. We confirmed that there appears to be a more pronounced reduction in the daily insulin dose during CSII therapy compared with glargine [11].

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