Med Clin (Barc). 2016;146(6):239–246

MEDICINA CLINICA

www.elsevier.es/medicinaclinica

Original article

Comparison between a multiple daily insulin injection regimen (basal once-daily glargine plus mealtime lispro) and continuous subcutaneous insulin infusion (lispro) using continuous glucose monitoring in metabolically optimized type 1 diabetes patients: A randomized open-labelled parallel study

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ARTICLE INFO

Article history:
Received 26 May 2015
Accepted 3 September 2015
Available online 4 December 2015

Keywords:
CSII
MDI
Type 1 diabetes

ABSTRACT

Background and objective: Advantages of continuous subcutaneous insulin infusion (CSII) over multiple daily injections with glargine (MDI/G) are still uncertain. We compared CSII vs. MDI/G therapy in unselected patients with type 1 diabetes using continuous glucose monitoring (CGSM). The primary end-points were glycaemic control and quality of life (QOL).

Methods: A total of 45 patients with long-term diabetes and mean HbA1c values of 8.6 ± 1.8% (70.5 ± 15.4 mmol/mol), previously treated with MDI/NPH, were switched to MDI/G for 6 months and then, unfulfilling therapy CSII indication, were randomly assigned to CSII or MDI/G for another six months. We evaluated QOL (EsDqol) and glycaemic control by measuring HbA1c levels, rate of hypoglycaemia, ketoacidosis and CGSM data.

Results: After the first phase (MDI/NPH to MDI/G) there was a significant improvement in total EsDQOL (99.72 ± 18.38 vs. 92.07 ± 17.65; $p < 0.028$), a 0.5% decrease in HbA1c values (8.4 ± 1.2 vs. 7.9 ± 0.7% [68 ± 9.7 vs. 63 ± 5.5 mmol/mol]; $p < 0.032$), an improvement in glycaemic variability (standard deviation 66.9 ± 14 vs. 59.4 ± 16 mg/dl; $p < 0.05$), a decrease in insulin requirements (0.87 ± 0.29 vs. 0.80 ± 0.25 U/kg; $p < 0.049$), a decrease in number of severe hypoglycaemia episodes (0.44 ± 0.9 vs. 0.05 ± 0.2; $p < 0.014$), and an increase in periods of normoglycaemia measured with CGSM (15.8 ± 10.9% vs. 23 ± 18.4%; $p < 0.003$). Six months after randomization, significant improvements were seen in the HbA1c (7.9 ± 0.7 vs. 7 ± 0.6% [63 ± 5.5 vs. 53 ± 4.5 mmol/mol]; $p < 0.001$) and EsQOL (91.66 ± 22 vs. 84.53 ± 1.63; $p < 0.045$) only in the CSII group. The HbA1c value was significantly lower when compared with the MDI/G group (CSII 7 ± 0.6% [53 ± 4.5 mmol/mol] vs. MDI/G 7.6 ± 0.9% [59.6 ± 7.7 mmol/mol]; $p < 0.03$).

Conclusions: Intensive insulin therapy with CSII vs. MDI/G was associated with better levels of HbA1c in patients with long-term type 1 diabetes.

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http://dx.doi.org/10.1016/j.medcli.2015.09.020
0025-7753/

Comparación entre múltiples dosis de insulina (insulina glargina una vez al día y lispro en las comidas) e infusión subcutánea continua de insulina con monitorización continua de glucosa en pacientes con diabetes tipo 1 metabólicamente optimizados. Estudio randomizado

Palabras clave:
ISCI
MDI
Diabetes tipo 1

R E S U M E N

Introducción y objetivo: Las ventajas de la infusión subcutánea continua de insulina (ISCI) sobre múltiples inyecciones diarias de insulina con glargina (MDI/G) son todavía inciertas. Comparamos ISCI frente a MDI/G en pacientes con diabetes tipo 1 sin indicación de terapia ISCI utilizando la monitorización continua de glucosa (CGSM). Los objetivos primarios fueron el control glucémico y la calidad de vida (QOL).
Métodos: Un total de 45 pacientes con diabetes 1 de largo tiempo de evolución y valores medios de HbA1c de 8,6 ± 1,8% (70,5 ± 15,4 mmol/mol), previamente tratados con MDI/NPH, fueron cambiados a MDI/G durante 6 meses y luego sin cumplir criterios clínicos para terapia ISCI asignados aleatoriamente a ISCI o MDI/G durante seis meses. Se evaluó la calidad de vida (EsDqol) y el control de la glucemia mediante la medición de los niveles de HbA1c, la tasa de hipoglucemias, cetoacidosis y datos de CGSM.
Resultados: Después de la primera fase (MDI/NPH a MDI/G) hubo una mejora significativa en EsDQOL total (99,72 ± 18,38 vs. 92,07 ± 17,65; p < 0.028), una disminución de 0,5% en los valores de HbA1c (8,4 ± 1,2 vs. 7,9 ± 0,7% [68 ± 9,7 vs. 63 ± 5,5 mmol/mol]; p < 0,032), una mejora en la variabilidad de la glucemia (desviación estándar 66,9 ± 14 vs. 59,4 ± 16 mg/dl; p <0,05), una disminución en las necesidades de insulina (0,87 ± 0,29 vs. 0,80 ± 0,25 U/kg; p <0,049), una disminución en el número de episodios de hipoglucemia grave (0,44 ± 0,9 vs. 0,05 ± 0,2; p <0,014), y un aumento en los periodos de normoglucemia medidos con CGSM (15,8 ± 10,9% vs. 23 ± 18,4%; p <0,003). Seis meses después de la aleatorización, se observaron mejoras significativas en la HbA1c (7,9 ± 0,7 vs. 7 ± 0,6%; [63 ± 5,5 vs. 53 ± 4.5 mmol/mol]; p <0,001) y la calidad de vida (91,66 ± 22 vs. 84,53 ± 1,63; p <0,045) sólo en el grupo ISCI. El valour de HbA1c fue significativamente menor en ISCI en comparación con el grupo MDI/G (CSII 7 ± 0,6% [53 ± 4,5 mmol/mol] vs. MDI/G 7,6 ± 0,9% [59,6 ± 7,7 mmol/mol]; p < 0,03).
Conclusiones: La terapia insulínica intensiva con ISCI vs. MDI/G se asoció con mejores niveles de HbA1c en pacientes con diabetes tipo 1 de larga evolución.

Introduction

Continuous subcutaneous insulin infusion (CSII) as therapy for patients with type 1 diabetes became available more than 30 years ago.[1] Since then several meta-analyses have reviewed multiple daily injections (MDI) therapy, most with MDI/NPH vs. CSII, discovering greater efficacy in glycaemic control with CSII therapy, in addition to a decrease in the incidence of hypoglycaemic events.[2–7] These meta-analyses established CSII therapy as the gold standard for insulin therapy in patients with type 1 diabetes. In addition, the relative benefit of CSII therapy over MDI/NPH is greater at higher baseline HbA1c values.[8] The limitations of MDI/NPH have been alleviated with the introduction of glargine, a long-acting insulin analogue with a flatter and more prolonged time-action profile.[9] Combined with rapid-acting insulin analogues, glargine provides better glycaemic control than intermediate-acting insulin NPH, with no increased risk of hypoglycaemia.[10,11] The question of whether CSII therapy with ultra-rapid insulin continues to be the gold standard in intensive insulin treatment for type 1 diabetes, however, is still not resolved.

Whereas several authors have found no difference between CSII and MDI with glargine in a variety of end-points, others have found CSII to be superior. Several randomized studies have performed a comparative evaluation of CSII vs. MDI with insulin glargine (MDI/G).[12–17] In adults, HbA1C results are similar with both treatments. However, in the study by Hirsch et al.[14] the results obtained from the measurement of serum levels of fructosamine and the reduced exposure to hyperglycaemia assessed through continuous glucose monitoring (CGMS) showed better metabolic control with CSII.

Severe hypoglycaemia remains one of the most feared complications.[18] The scientific evidence that CSII therapy reduces the frequency of severe hypoglycaemia compared to MDI/NPH is very strong.[19] Pickup and Keen,[2] in their review, found that the rate of severe hypoglycaemia was four times lower with CSII than with MDI, and the greatest improvements occurred in those patients with higher rates of severe hypoglycaemia when treated with MDI. The frequency of mild hypoglycaemia is also lower with CSII, with a reduction of 75% after switching from MDI.[20] Several studies comparing MDI based on glargine or detemir have found a lower incidence of nocturnal hypoglycaemia than with NPH.[21] On the other hand, studies comparing the incidence of severe hypoglycaemia during CSII and MDI with long-acting analogues have given contrasting results, with some finding no difference[14,15,17] while others found that patients prone to hypoglycaemia had fewer hypoglycaemic episodes during CSII.[20]

Currently there is strong interest in glycaemic variability, due to the possible relationship with microvascular and macrovascular disease.[22,23] Indeed, glycaemic variability in combination with HbA1c could be a more realistic indicator of glycaemic control and long-term risk of complications than HbA1c alone.[24,25] Several authors found that glucose variability during CSII was smaller than during MDI/NPH.[26,27] Other studies have compared the effects on glucose variability of CSII and MDI based on long-acting analogues and have found either no differences, or higher or lower glucose variability[12,14,16,28–30] during CSII.

There are conflicting results concerning the effects of CSII therapy on quality of life. A meta-analysis in 2007 concluded that the effects of CSII on quality of life remain unclear.[31] More recent studies have obtained different results, some finding a better quality of life[15,27,32] but others seeing a similar quality of life with CSII.[17]

The objectives of this study were to determine: (1) whether CSII is more effective than MDI therapy using insulin analogues (rapid and long) in metabolic control and QOL, and (2) whether CSII therapy has supplemental benefits in patients with type 1 diabetes who are optimized with MDI therapy using insulin analogues.

Materials and methods

This was a randomized, parallel group, open-label study performed in the Diabetes Centre of the Endocrinology and Nutrition Department of Carlos Haya University Hospital in Malaga, Spain.

Subjects

Inclusion criteria: patients aged 18–65 years with type 1 diabetes for more than 5 years.

Exclusion criteria: acute coronary syndrome or stroke in the last 6 months, active proliferative retinopathy, uncontrolled hypertension, severe vegetative neuropathy, impaired hepatic/renal function, prior use of CSII or insulin glargine, patients unable to use CSII or MDI or patients planning pregnancy.

A total of 45 patients met the inclusion criteria.

The sample size calculation was performed to detect a difference of 1.5% in HbA1c using a standard deviation of 1.2, a $\alpha = 0.05$ (two-tailed), and a power of 90%. The resulting minimum size was 15 patients per group, including 15% of lost patients. To obtain 30 patients (15 CSII and 15 MDI/G) 45 is selected in case had lost over 15% calculated on the protocol development. The key is the intergroup comparison (CSII vs. MDI/G) and is carried out at 12 months.

During the first 6 months seven patients were lost, leaving 38 patients; then, without meeting criteria for CSII therapy, these 38 patients were randomized, 15 to CSII and 23 to MDI/G during six months, with no patients lost in this phase. The 7 patients withdrawing of the study at the first phase owed to the inability to follow protocol and monthly visits.

All the subjects provided written informed consent. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and with the approval of the Ethics Committee of Carlos Haya University Hospital.

Design

Randomized clinical trial (2 MDI/G: 1 CSII) with a prior homogenization phase with MDI/G.

- Phase 1: educational homogenization and adherence.
  Forty-five patients with type 1 diabetes, under treatment with MDI/NPH and rapid analogues, were switched to MDI with glargine as basal insulin and followed-up monthly for 6 months. The patients used insulin lispro (Eli Lilly Inc., Indianapolis, IN) before each meal and a single dose of glargine. Seven patients dropped out of the study in Phase 1.
- Phase 2: randomization. After the first 6 months, from this metabolically optimized group, 15 patients were randomly assigned to CSII therapy. These CSII patients received insulin lispro via a multi-programmable insulin infusion system (Paradigm 712, Medtronic, USA). 23 patients continued with MDI/G once daily in the evening plus mealtime insulin lispro; both groups completed 6 further months (23 patients MDI/G vs. 15 patients CSII), with monthly follow-up.

All the patients developed skills necessary for intensive functional therapy including self-monitoring of blood glucose (SMBG) using a plasma-calibrated memory glucose metre (OneTouch Ultra; Lifescan, Milpitas, CA), carbohydrate counting, insulin adjustment and technical aspects of the pumps. The glycaemic targets were identical for both treatment groups: glycaemia of 80–120 mg/dl (4.4–6.6 mmol/L) before and <150 mg/dl (8.3 mmol/L) 2 h after meals. Three days of glycaemia monitoring via CGSM (Medtronic, USA) was done at the end of each treatment period and the time spent with blood glucose < 70 mg/dl/3.9 mmol/L, >180 mg/dl/10 mmol/L, and 70–180 mg/dl/3.9–9.9 mmol/L was recorded.[33]

Variables and instruments

- Sociodemographics: sex and age.
- Anthropometric: weight, BMI.
- Insulin therapy: daily insulin dose (DID) (insulin/kg), basal insulin dose (%), bolus insulin dose (%)
- Complications: mild hypoglycaemia (episodes per week), severe hypoglycaemia (episodes per 6 months) and ketoacidosis episodes. Hypoglycaemia was defined according to the ADA criteria.[34]
- Metabolic control parameters: HbA1c (HPLC; Diabetes Control and Complications Trial [DCCT] Research Group aligned).
- Glycaemic variability parameters: obtained by standard deviation (SD), low blood glucose index (LBGI) and high blood glucose index (HBGI),[35] obtained from CGSM.
- Quality of life parameters: the quality of life during each treatment phase was measured using a version of the Diabetes Quality of Life (EsDQOL) questionnaire of the DCCT Research Group, adapted to the Spanish population.[36] The scale consists of 43 items that are 4 dimensions: satisfaction with treatment (15 items), impact of treatment (17 items), social/vocational concerns (7 items) and concern regarding the future effects of diabetes (4 items). Each item has 5 possible answers on Likert scoring from 1 to 5. Satisfaction subscale responses to each item ranged from "very satisfied" (1 point) to "not satisfied" (5 points). In the other three subscales, responses ranged from "never" (1 point) to "always" (5 points). A total score and subscales score can be obtained. A lower score means better quality of life. It is designed to be self-administered.
- The primary objectives were the HbA1c value at the end of each treatment phase, with a goal of HbA1c <7.5% and the QOL during each phase.

Data analysis and statistics

The data are presented as mean ± SD or proportions. At baseline, homogeneity between the randomized sequence groups (CSII and MDI/G) was tested using two-sample unpaired Student's *t*-test for normally distributed data, or the Wilcoxon rank sum test for non-normally distributed data. To compare the scores before and after treatment two types of analysis were used. For the variables with scores that adjusted to a normal distribution a repeated measures ANOVA was used. For the variables with scores that did not follow a normal distribution a non-parametric contrast test was used (Wilcoxon test). For comparison of means the Student *t* test was used for related or independent samples and the chi-square test was used to determine the association between qualitative variables. Analyses per protocol were done and carried out with SPSS software (18.0 version). The confidence intervals were set at 95%.

Results

Baseline data (Table 1)

The mean age of patients was 29.8 ± 8.5 years, 46% were men, the duration of diabetes was 13.7 ± 7 years, the mean HbA1c was 8.4 ± 1.2% (68 ± 9.7 mmol/mol), 33% with <7.5% (58.5 mmol/mol). The baseline characteristics were similar for both treatment groups.

Table 1
Baseline characteristics at start of treatment.

	Total $N=38$	MDI/G $N=23$	CSII $N=15$	p
Age (years)	29.8 ± 8.5	28 ± 7	31 ± 10	ns
Gender (men/women)	21/24	15/15	6/9	ns
Years with diabetes	13 ± 7	12.3 ± 6	16 ± 8	ns
Body mass index (kg/m^2)	25 ± 3.5	24.9 ± 3.7	26 ± 3.3	ns
Daily insulin dose/kg	0.87 ± 0.2	0.87 ± 0.2	0.87 ± 0.3	ns
Mild hypoglycaemia/week	3.04 ± 3.4	3.03 ± 3.6	3.07 ± 3	ns
Severe hypoglycaemia/6 months	0.44 ± 0.9	0.43 ± 1.1	0.46 ± 0.8	ns
SMBG/day	3 ± 1.2	2.8 ± 1	3.2 ± 1.6	ns
HbA1c % (mmol/mol)	8.4 ± 1.2 (68 ± 9.7)	8.3 ± 1.2 (67.2 ± 9.7)	8.5 ± 1.2 (69.4 ± 9.7)	ns
Ketoacidosis (previous 6 months)	2 cases	1	1	ns
Hospitalization (previous year)	4 cases	2	2	ns
Preproliferative retinopathy	5 cases	4	1	ns
Proliferative retinopathy	7 cases	3	4	ns
Incipient nephropathy	3 cases	2	1	ns
Established nephropathy	2 cases	2	0	ns
Unawareness hypoglycaemia	2 cases	1	1	ns
Hypertension	8 cases	6	2	ns

ns, not significant.

Phase 1: homogenization (Table 2)

Metabolic control: in the first 6 months (MDI/NPH to MDI/glargine) ($n=38$), there was an improvement in HbA1c, with a mean decrease of 0.5% (8.4 ± 1.2% vs. 7.9 ± 0.7%; $p<0.032$) (Fig. 1), a HbA1c <7.5% was reached by 36.8% of the patients (vs. 33% at baseline; $p<0.7$) and the frequency of severe hypoglycaemia declined (0.44 ± 0.9 vs. 0.050 ± 0.2; $p<0.014$) with no changes in mild hypoglycaemia. There was an increase in the number of self-analyses per day (3 ± 1.2 vs. 4.33 ± 1.5; $p<0.0001$) and an increase in BMI (25.4 ± 3 vs. 25.9 ± 3.5; $p<0.014$). The total daily insulin decreased 8% (0.87 ± 0.29 vs. 0.80 ± 0.25 IU/kg; $p<0.049$) and basal insulin decreased 12% (41.8 ± 16.4 vs. 36.8 ± 15.7 IU/day; $p<0.001$). There were no episodes of ketoacidosis in the group. With respect to the CGMS data, there was an increase in periods of normoglycaemia (15.8 ± 11% vs. 23 ± 18.4%; $p<0.03$) and a significant improvement in glycaemic variability measured by the SD of CGMS (66.9 ± 14 vs. 59.4 ± 16; $p<0.05$).

Quality of life: significant changes were perceived in the overall EsDQOL (99.72 ± 18.38 vs. 92.07 ± 17.65; $p<0.007$) (Fig. 2) and an improvement in the subscale "satisfaction with treatment" (39.15 ± 8.54 vs. 35.45 ± 7.46; $p<0.01$).

Phase 2: after randomization (Table 2)

Metabolic control: In the CSII group, after 6 months HbA1c values decreased significantly (7.9 ± 0.7% [63 ± 5.5 mmol/mol] to 7 ± 0.6% [53 ± 4.5]; $p<0.00$) (Fig. 1), with 67% of patients achieving the objective of 7.5% (vs. 6 m: 36.8%) ($p=0.5$). There was an improvement in time in normoglycaemia (23 ± 18.4 vs. 50 ± 1.6%; $p<0.002$), time in hyperglycaemia (69.4 ± 21.5 vs. 42.3 ± 12%; $p<0.02$) and HBGI (CGMS) (8.1 ± 4.5 vs. 5.4 ± 0.3; $p<0.045$).

In the MDI/G group, no significant change was seen in HbA1c (Fig. 1). In CGMS, decreases were seen in mean glycaemia (162 ± 30 mg/dl vs. 146.78 ± 36; $p<0.04$), and time in

Table 2
Comparative analysis between the homogenization and randomization phases.

	Homogenization phase			Randomized study		
	Basal MDI/NPH	6 months MDI/glargine	p	12 months MDI/glargine	12 months CSII	p
N	38	38		23	15	
Body mass index	25.4 ± 3.5	25.9 ± 3.5	0.014	25.8 ± 3.5	26.8 ± 3.5	0.42
Basal insulin dose (IU/day)	41.8 ± 16.4	36.8 ± 15.7	0.001	34.7 ± 12.5	34.34 ± 18.66	0.9
Total insulin dose (IU/kg/day)	0.87 ± 0.29	0.80 ± 0.25	0.049	0.77 ± 0.24	0.78 ± 0.21	0.9
HbA1c % (mmol/mol)	8.4 ± 1.2 (68 ± 9.7)	7.9 ± 0.7 (63 ± 5.5)	0.032	7.6 ± 0.9 (59.6 ± 7.7)	7 ± 0.6 (53 ± 4.5)*	0.03
HbA1c <7.5% (58.5 mmol/mol)	33%	36.8%	0.7	52%	67%	0.46
SMBG/day	3 ± 1.2	4.3 ± 1.5	0.000	3.2 ± 1.4	4.7 ± 1.7	0.008
Severe hypoglycaemia	0.44 ± 0.9	0.050 ± 0.2	0.014	0.05 ± 0.2	0.29 ± 1	0.08
CGMS						
Mean glycaemia	172.2 ± 42	162 ± 30	0.104	146.78 ± 36#	145 ± 20	0.9
Standard deviation	66.9 ± 14	59.4 ± 16	0.05	58 ± 13	65 ± 24	0.2
% normoglycaemia	15.8 ± 10.9	23 ± 18.4	0.03	50.7 ± 18#	50 ± 13.6*	0.84
% hypoglycaemia	8.3 ± 9.5	7.3 ± 7.9	0.56	9.4 ± 8.4	7.6 ± 8	0.4
% hyperglycaemia	73.7 ± 21.2	69.38 ± 21.47	0.30	43 ± 16.2#	42 ± 12*	0.88
LBGI	2.1 ± 2.3	1.8 ± 1.8	0.42	2.74 ± 2.24	2.89 ± 2.56	0.3
HBGI	9.7 ± 5.6	8.1 ± 4.5	0.32	6.8 ± 4.6	5.4 ± 3*	0.06
DQOL	99.72 ± 18.38	92.07 ± 17.65	0.007	92.78 + 20.83	84.5 ± 18*	0.2
Satisfaction	39.15 ± 8.4	35.45 ± 7.46	0.00	35.08 + 6.74	30.53 + 9.27	0.08
Impact	34.94 ± 6.5	33.48 ± 7.5	0.219	33.39 + 10.99	31.80 + 6.06	0.613
Social concerns	14.8 ± 5	14.21 ± 5.2	0.317	14.34 + 5.27	13.26 + 4.38	0.514
Worry about future	10.35 ± 2.8	10.1 ± 2.69	0.582	9.95 + 3.61	8.93 + 2.25	0.335

# $p<0.05$ MDI/G 6 M vs. MDI/G12 M.
* $p<0.05$ MDI/G 6 M vs. CSII 12 M.

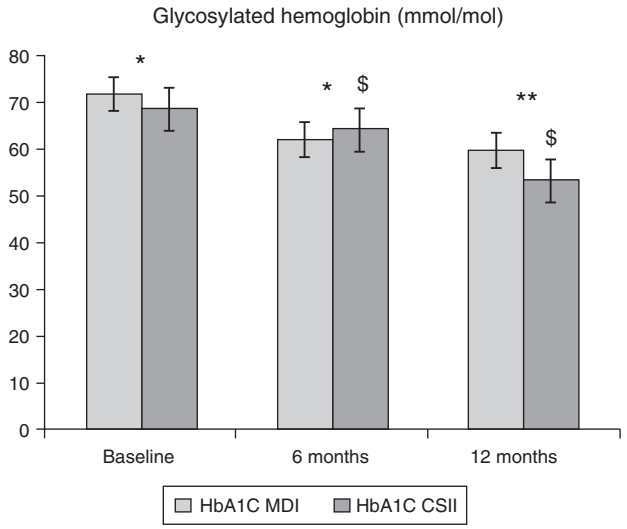

Fig. 1. HbA1c at baseline, and after 6 and 12 months with MDI and CSII. *$p < 0.05$ basal–6 month in 2 groups; **$p < 0.05$ 6 month–12 month in CSII group; \$$p < 0.05$ MDI/G vs. CSII 12 month.

hyperglycaemia (69.38 ± 43.16 vs. $43 \pm 16.2\%$; $p < 0.01$) and an increase in time in normoglycaemia (23 ± 18.4 vs. $50.7 \pm 18\%$; $p < 0.01$).

Although a tendency towards better control parameters was seen in the metabolic variables evaluated in the two groups, significantly lower levels of HbA1c were only seen in the CSII group compared with the MDI/G group (MDI/G 7.6 ± 0.9 vs. CSII $7 \pm 0.6\%$; $p < 0.03$), with a higher number of self-tests per day in the CSII group compared to the MDI/G group: 4.7 ± 1.6 vs. 3.2 ± 1.5 ($p < 0.008$). There is a positive correlation in the set of the 38 patients at 12 months between the number of SMBG and reached HbA1c ($r = -0.45$, $p = 0.005$.) which does not occur in each group independently (MDI/G $r = 0.3$; $p = 0.13$; CSII $r = 0.4$; $p = 0.14$).

No changes were seen in BMI, insulin dose, mild or severe hypoglycaemia or episodes of ketosis or ketoacidosis in the two groups.

Quality of life: the total DQOL score decreased significantly in the CSII group (91.66 ± 22 to 84.53 ± 1.63; $p < 0.045$) (Fig. 2). The differences between groups (CSII vs. MDI/G) in absolute scores for total DQOL and the subscales were not significant.

There were no serious adverse events during the study.

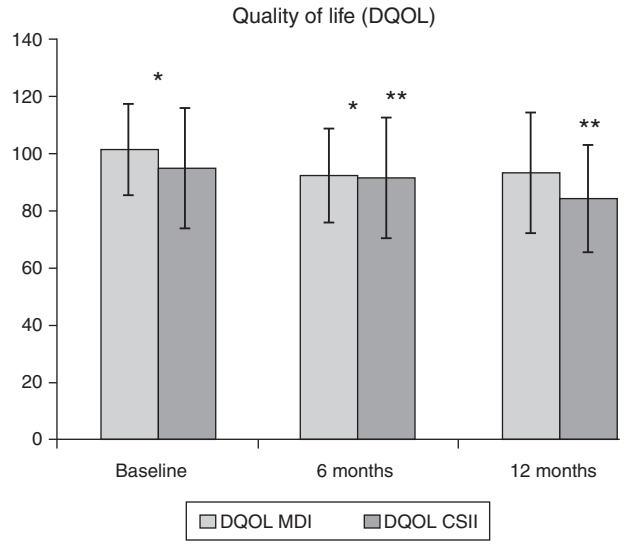

Fig. 2. DQOL at baseline, and after 6 and 12 months with MDI and CSII. *$p < 0.05$ basal–6 month in 2 groups; **$p < 0.05$ 6 month–12 month in CSII group.

Discussion

For many years, the advantages of CSII therapy made it a superior treatment compared with MDI/NPH. The incorporation of the long-acting analogues glargine and detemir, soluble insulins with a more predictable absorption, more stable blood levels and with the possibility of improving glycaemic control, have now raised the question of whether these new insulins can replace the need for CSII in people with type 1 diabetes.

The factors that have an impact on metabolic improvements associated with CSII therapy are still poorly known. Dependency upon pre-CSII results after switching could help to explain the discrepancies regarding the efficacy of the prior studies comparing MDI and CSII. In our study the sample was metabolically optimized during the first 6 months with MDI/G, with the aim of later comparing both therapeutic options randomly.

Sufficient scientific evidence exists to assert that CSII therapy is superior to MDI/NPH in addressing three problems: (1) elevated HbA1c; (2) repetitive severe hypoglycaemia and (3) glycaemic fluctuations.[37] However, what is the situation with MDI/G?

Metabolic control

Combined with rapid-acting insulin analogues, glargine provides better glycaemic control than NPH, without increasing the risk of hypoglycaemia.[10,11] Our findings are in agreement with these previous publications. In the first 6 months we detected a significant change in HbA1c upon switching from MDI/NPH to MDI/G, with a significant increase in periods of normoglycaemia and SD, and a significant decrease in episodes of severe hypoglycemia. We also found a significant increase in the number of self-tests per day due to the intensification of the insulin treatment with structured re-education and monthly visits. There was a decrease in daily total and basal insulin and an increase in BMI, probably in relation to the overall metabolic improvement.

A systematic review published in 2012 of randomized studies[38] concluded that CSII provides better HbA1c than MDI, with a low level of evidence. Some of these studies performed a comparative evaluation of CSII vs. MDI with insulin glargine (MDI/G).[12–17] However, only two randomized studies, one in adolescents[12] and the other in adults,[14] although of short duration, were able to confirm that CSII therapy may improve glycaemic control when compared to MDI with analogues. Doyle et al.[12] randomized 32 adolescents with type 1 diabetes to MDI/G or CSII for 16 weeks and reported a decrease in HbA1c in the CSII group. Hirsch et al.[14] randomized 100 patients with type 1 diabetes to MDI/G or CSII for 5 weeks and demonstrated both a decrease in fructosamine as well as a decrease in the area under the glucose curve using CGMS. In our study, the CSII group achieved better HbA1c than the MDI/G group after 6 months, but no differences were found in the other variables.

To the best of our knowledge, this is the first randomized study in adult patients to report better HbA1c with CSII therapy vs. MDI/G in a maximally optimized adult group and with a prolonged follow-up of 6 months.

In a recent paper derived of the large database of the T1D Exchange clinic registry, Miller et al.[39] communicate that a higher number of SMBG measurements per day were associated with non-Hispanic white race, insurance coverage, higher household income, and use of an insulin pump for insulin delivery ($p < 0.001$ for each factor). After adjusting for these factors, a higher number of SMBG measurements per day was strongly associated with a lower HbA_{1c}

level (adjusted $p < 0.001$), with the association being present in all age-groups and in both insulin pump and injection users.

Was there an association between the frequency of SMBG and changes in HbA1c in our study? In this study the frequency and timing of SMBG measurements for study purposes with a structured SMBG regimen was used. Patients in the intensive MDI/G treatment made an average 3.2 ± 1.4/day while the demands of CSII therapy are always greater and patients CSII group made an average of 4.7 ± 1.7, thus we cannot rule out that the differences in the two groups of intensive insulin treatment relates to the number of different daily self-analysis performed and better treatment settings. This may be part of the advantages of this intensive treatment.

Hypoglycaemia

As very strong evidence exists that CSII therapy reduces the frequency of severe hypoglycaemia compared with MDI/NPH therapy, this clinical problem is the main indication in many countries.[19] Pickup and Keen[2], in their meta-analysis, found that the rate of severe hypoglycaemia was four times lower with CSII than with MDI, and the greatest improvements occurred in those patients with higher rates of severe hypoglycaemia when treated with MDI. Long-acting analogues, however, with their improved predictability and flatter absorption profile can lower the frequency of hypoglycaemia.[21] In fact, these functional strategies must be used and explored in patients with poor metabolic control before initiating CSII treatment. Our study confirms this because we reported a significant decrease in severe hypoglycaemia after switching from MDI/NPH to MDI/G. Studies comparing the incidence of severe hypoglycaemia during CSII and MDI based on short- and long-acting analogues have given contrasting results, some finding no difference[14,15,17] while others found that patients prone to hypoglycaemia had fewer hypoglycaemic episodes during CSII.[20] In our study, no significant differences in episodes of severe hypoglycaemia were found between the MDI/G group and the CSII group, and no significant changes were seen in mild hypoglycaemia in either treatment phase.

Glycaemic variability

Glycaemic variability is included as an indication for treatment with CSII in some references[40] but not in others.[19] CSII should control glucose variability better than any MDI regimen, because during CSII the basal rate of insulin administration can be adjusted continuously and because the constant delivery of small amounts of insulin should minimize glucose oscillations.

Several authors have found that glucose variability during CSII was smaller than during MDI with NPH.[26,27] On the other hand, other studies have compared the effects on glucose variability of CSII and MDI based on long-acting analogues and have found either no difference, or higher or lower glucose variability during CSII.[12,14,16,29,30] It should be noted, however, that the studies differed for patient selection, degree of metabolic control at study entry and the methods used to measure variability. A few studies have investigated this aspect using continuous glucose monitoring systems, but with differing results.[16,29,30] Some found more variability with CSII[29] but others concluded that glucose variability was lower in CSII when glucose control was good (HbA1C < 7.5%).[16,30] Clearly, more work is needed on this important subject.

In the present study, the variables of glucose variability (SD, LBGI and HBGI of CGSM data) were evaluated every 6 months. In the switch from MDI/NPH to MDI/G we reported less glycaemic variability according to the SD of CGSM, which was not repeated after randomization when comparing MDI/G vs. CSII. Given the limited value that this measurement has for the overall evaluation of glycaemic variability and the low number of patients we cannot provide a conclusive result.

Quality of life

Quality of life is an important criterion in decision making, but difficult to quantify.

In a recent revision, Barnard et al.[31] systematically evaluated 18 articles that met adequate inclusion criteria and concluded that the effects of CSII on quality of life remain unclear.

In our study, during the first phase of treatment (NPH to MDI/G) an improvement was noted in the DQOL, at the expense of the subscale "satisfaction with treatment." After randomization, as occurred with HbA1c, the capacity of MDI/G to improve QOL appeared to have reached its limit during the first 6 months and in the following months no changes were reported in the MDI/G group. However, CSII therapy, as with HbA1c, goes further in improving QOL. These results differ from another Spanish study by Lozano-Serrano et al.,[41] who found no differences between CSII and MDI using the same test as in our study (the Spanish version of the Diabetes Quality of Life specific for diabetes related ESQOL), though our results are nevertheless in agreement with other publications. The systematic review of randomized studies published in 2012[37] concluded that CSII achieves a better QOL than MDI, but with a low level of evidence.

The most robust study to date is by Hoogma et al.[27], with 272 randomized patients in 5 countries treated either with MDI/NPH or CSII and assessed via DQOL, SF-12 and an additional questionnaire evaluating lifestyle, manageability of the disease and acceptability of the types of treatment, which were better for the group of patients using pumps.

In adults, only 5 randomized studies have measured quality of life using different questionnaires for CSII vs. MDI,[15,17,27] though only 2 with MDI/G,[15,17] and have obtained different results. Bolli et al.[15], using the diabetes treatment satisfaction questionnaire (DTSQ), found a better quality of life in the CSII group, but Thomas et al.[17], using the DQOL, found no differences after 6 months of follow up. Nicolucci et al.[42], in a large (1341 patients), multicentre, case–control study, reported comparative data on QOL for MDI (90% glargine) and CSII. They used the DQOL, DTSQ and the SF-36 Health Survey. Their results suggest that gains in QOL in the CSII group came from greater flexibility, less fear of hypoglycaemia and higher satisfaction with treatment.

Strengths and limitations

The principal limitation of this study is the small sample size, due mainly to the lack of finance for more CGMS and CSII, which might then have revealed more differences. Concerning the study design, contacts between participants and healthcare providers were more frequent than in normal daily life. This may diminish the external validity of the study, but reinforces the conclusion that CSII could be better than MDI/G even under strict conditions of patient follow-up.

The strengths of this study are the incorporation of CGMS to evaluate both treatments and the initial homogenization phase, with a group of motivated and metabolically optimized patients in whom it was difficult to show improvements and who were not usual candidates for CSII. The subsequent randomization enabled us to eliminate any personal bias in the differences found between the two alternative therapies. And finally, a prolonged follow-up of 6 months for each phase of the trial controlled the "dragging" phenomenon of some of the variables studied.

Conclusions

To the best of our knowledge, this is the first randomized study in adult patients to find better HbA1c with CSII therapy vs. MDI/G in a maximally optimized adult group and with a prolonged follow-up of 6 months, with no worsening in the other metabolic variables (weight, mild, severe hypoglycaemia) and QOL.

Further studies are needed to define the impact on glycaemic variability and QOL and to establish groups of patients who would benefit from this therapy, as well as determine the most cost-effective indications for this therapeutic alternative.

Conflict of interests

The authors declare no conflict of interest.

Acknowledgements

This study was undertaken with finance from the Fondo de Investigación Sanitaria (ISCIII) (PI07/90330), Junta de Andalucía (0240/2006).

We acknowledge other collaborations:

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