Insulin-pump use in everyday practice: Data from an exhaustive regional registry in France


For Groupe Pompe Sud-Francilien

Abstract

Aim. – The aim of this study is to evaluate the effectiveness and safety of continuous subcutaneous insulin infusion (CSII) under real-life conditions among all patients treated with CSII in the south of Paris.

Methods. – The 42 diabetologists practising in the region enrolled all patients treated with CSII or admitted for CSII initiation. During the study visit, the data for pump use and clinical results were recorded.

Results. – Data were obtained for 424 patients, mean age 44.2 ± 15.6 years, disease duration 18.7 ± 10.6 years, including 339 treated with CSII for longer than three months (mean duration: 3.5 ± 3.5 years; range: 3–258 months). Most of the patients (N = 285, 84.8%) had type 1 diabetes; 44 (13.1%) had type 2 diabetes. In patients treated for more than three months, HbA1c decreased significantly between CSII initiation (9.1 ± 1.9%) and the study visit (7.8 ± 1.4%; P < 0.0001). Patients with HbA1c > 9%, using the pump, experienced a significant 0.9% improvement in their HbA1c levels with CSII versus multiple daily injections (P = 0.001). The number of episodes of moderate hypoglycaemia was 2.7 ± 2.5 per patient per week; of severe hypoglycaemia, 0.34 per patient per year and of ketoacidosis, 0.11 per patient per year. Factors significantly associated with HbA1c levels included amount of physical activity, pregnancy, HbA1c at CSII initiation and number of glucose self-determinations. Those associated with the number of moderate hypoglycaemia episodes were basal rate number, female gender and HbA1c level. HbA1c was negatively correlated with moderate hypoglycaemia (P < 0.001), but not with severe hypoglycaemia.

Conclusion. – This ‘pump’ registry establishes the effectiveness of CSII in everyday practice, yet underscores the risks of severe hypoglycaemia and ketoacidosis episodes. It could help diabetologists to improve patient training programmes and follow-up.

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Résultats. – Quatre cent vingt-quatre patients, âgés de 44,2 ± 15,6 ans, diabétiques depuis 18,7 ± 10,6 ans, ont été inclus. Trois cent trente-neuf étaient traités depuis plus de trois mois (3,5 ± 3,5 ans, 3–258 mois). Deux cent quatre-vingt-cinq patients avaient un diabète de type 1 (84,8 %); 44 (13,1 %) avaient un diabète de type 2. Chez ceux traités depuis plus de trois mois, l’HbA1c a significativement diminué (multi-injections : 9,1 ± 1,9 % versus pompe : 7,8 ± 1,4 %, P < 0,0001). Les patients dont l’HbA1c était supérieure à 9 % sous pompe, avaient une amélioration significative de 0,9 % de l’HbA1c, par rapport au traitement par multi-injection (P = 0,001). Le nombre d’hypoglycémies modérées était de 2,7 ± 2,5 par patient par semaine, celui des hypoglycémies sévères de 0,34 par patient par année et celui des acidoctoses de 0,11 par patient par année. Les facteurs associés à une HbA1c correcte étaient l’activité physique, la grossesse, une bonne HbA1c à la mise sous pompe et le nombre d’autocontrôles glycémiques. Les facteurs associés au nombre d’hypoglycémie sévère et d’acidoctose ce qui devait permettre d’améliorer l’éducation et le suivi de ces patients.

Conclusion. – Ce registre exhaustif confirme l’efficacité du traitement par pompe à insuline en pratique clinique mais souligne le risque d’hypoglycémie sévère et d’acidoctose ce qui devait permettre d’améliorer l’éducation et le suivi de ces patients.

Keywords: Diabetes; CSII; HbA1c; Register

Mots clés : Diabète ; Pompe à insuline ; HbA1c ; Registre

The Diabetes Control and Complications Trial established that tight glucose control slowed the progression of long-term complications of type 1 diabetes mellitus [1]. Continuous subcutaneous insulin infusion (CSII) using a fast-acting insulin analogue is the most effective means of achieving glucose control. In several studies, CSII produced significantly lower HbA1c values than did multiple daily injections (MDI), with no increases in episodes of hypoglycaemia or ketosis [2–6]. In addition to being more effective than MDI, CSII was safe when used with close monitoring in selected patients and, indeed, intensive monitoring programmes were implemented in these prospective studies. The safety and effectiveness of CSII in patients with type 1 diabetes treated in everyday practice are unknown. For this reason, a CSII registry was recently set up in the southern part of the Île-de-France area, near Paris (France), to collect data on all patients treated with CSII in everyday practice, a population that may differ substantially from the selected and closely monitored populations included in clinical studies. The immediate objectives of the registry are to evaluate the effectiveness and safety of CSII, the quality of life of patients using CSII and the quality of medical device vigilance under real-life conditions. In the long term, the further objectives are to collect prospective data on medical device vigilance and to monitor changes over time. The baseline characteristics of the patients in the registry are detailed here.

1. Patients and methods

The registry contains data on all diabetic patients treated with CSII in the sud-francilienne region of France (immediately south of Paris). The 42 diabetologists practising in the region (in 17 hospitals or in private practices) enrolled all patients who were treated with CSII or admitted for CSII initiation between January 2005 and June 2006. Patients who had moved to another region or had died were not included in the registry. Patients were identified through database searches at each hospital and private practice in the region, as well as through information from suppliers of the infusion sets, reservoirs and batteries used with insulin-pumps. Each patient was given an appointment over the phone for the study visit; patients who missed their appointment were called again. Patients who were included in the study, but failed to attend the study visit despite four phone calls were considered lost to follow-up. During the study visit, the following data were recorded: age, gender, years of formal education and occupational status; type, duration and complications of diabetes; type of pump, insulin doses, basal insulin rate, number of boluses, type of boluses (standard, square-wave or combination), timing of boluses (before, during or after meals, or double boluses); infusion-set tolerance and glucose control data, including HbA1c, mean number of episodes of moderate hypoglycaemia (defined as those in which correction required self-administration of oral sugar) within the last week, as reported by the patient or entered in the patient’s diary, mean number of episodes of severe hypoglycaemia (defined as those in which correction required help from another person), number of episodes of ketosis as reported by the patient and number of episodes of ketoacidosis. The patient was asked to complete three visual analogue scales (VAS) evaluating discomfort related to the catheter, acceptability of the pump and satisfaction with glucose control. The data collection forms were sent to the study centre and entered into a database. Longstanding CSII was defined as CSII started at least three months before study inclusion.

1.1. Statistical analysis

To analyze the data collected at study inclusion, we used SPSS version 12.0F (SPSS, Chicago, IL). Data are given as means ± S.D. Percentages were determined using the number of responses as the denominator. Wilcoxon’s rank test for paired samples was performed to compare HbA1c levels at CSII initiation and at the study visit. Correlations between quantitative variables were evaluated using Spearman’s rank test and the Kruskal–Wallis rank test used for correlations between quantitative and qualitative variables. A generalized linear model was used to conduct an overall assessment of the link between HbA1c or the weekly number of hypoglycaemic episodes and the variables correlated with these factors. In all tests, P values equal to or less than 0.05 were considered significant.
2. Results

2.1. Study population

We identified 458 patients treated with CSII in the study region, among whom, 14 had left the region since starting CSII, leaving 444 patients for inclusion in the registry. Data were obtained for 424 of these patients. The data collection forms for seven patients were completed, but not sent to the study investigators and 13 patients failed to keep their appointment for the study visit despite multiple phone calls. Thus, the registry cohort represents 95.4% of the patients treated with CSII in the study region.

Of these 424 patients, 339 had been using CSII for more than three months at the time of the study visit. Among these patients on longstanding CSII, the mean age was 44.2 ± 15.6 years and mean disease duration was 18.7 ± 10.6 years. Most of the patients (N = 285; 84.8%) had type 1 diabetes, although 44 (13.1%) had type 2 diabetes (including three with mature-onset diabetes of the young), six (1.8%) had diabetes due to chronic calcifying pancreatitis, one (0.3%) had mitochondrial diabetes and three (0.9%) had diabetes of unknown origin. The reason for using CSII was poor glucose control (HbA1c > 8%) in 44.2% of patients, frequent hypoglycaemic episodes in 33.6%, pregnancy (initial indication) in 13.0%, intolerance to insulin injections in 4.8%, insulin resistance in 2.7% and an irregular lifestyle in 1.5%. Their mean time using CSII was 3.5 ± 3.5 years (range 3–258 months) and exceeded five years in 21% of patients. Years of education were: less than 9, 6.7% of patients; nine completed years, 17.6%; vocational degree, 30.4%; 10–12 years of formal schooling, 4.9%; high school completed, 15.2%; 2–3 years of university education, 15.2% and university degree, 10%. Mean number of blood glucose determinations was 28.1 ± 15.9 per week (4.0 ± 2.3 per day).

The characteristics of the 105 patients who started CSII within the last three months were not significantly different from those of the longstanding CSII group. At inclusion into the registry, 10 (2.94%) patients were pregnant.

2.2. Diabetes control

In the 339 patients with longstanding CSII use, mean HbA1c decreased significantly between CSII initiation (9.1 ± 1.9%) and the study visit (7.8 ± 1.4%; P < 0.0001) (Fig. 1A). At the study visit, HbA1c was less or equal to 7% in 28% of patients, 7.1–7.5% in 23%, 7.6–8% in 16%, 8.1–9% in 22% and greater or equal
to 9% in 11% (40 patients). Mean HbA1c in these latter 40 patients was 10.4 ± 1.5% at the study visit and had been significantly higher before starting CSII (11.3 ± 2.0%; P = 0.001) (Fig. 1B). Thus, these patients experienced a significant 0.9% improvement in their HbA1c levels with CSII compared with their previous MDI regimen.

Overall, in this population with longstanding CSII use, the mean number of episodes of moderate hypoglycaemia was 2.7 ± 2.5 per patient per week and the mean number of episodes of severe hypoglycaemia was 0.34 per patient per year. Severe hypoglycaemia occurred in 64 patients, including three who each reported ten episodes of severe hypoglycaemia within the past year. The mean number of episodes of ketosis within the last three months was 0.26 ± 0.97 and the mean number of episodes of ketoacidosis was 0.11 per patient per year. Ketoacidosis occurred in 23 patients, including 18 who experienced a single episode, three who had three episodes each and two who had six episodes each.

2.3. Use of pump and infusion sets

2.3.1. Pump

Pump brands and models used by the 339 patients with longstanding CSII use were: MiniMed 508®, 142 patients; Paradigm 512/712®, 105 patients; HTRON V100®, 17 patients; DTRON®, 28 patients; Cozmo®, 44 patients and not recorded, three patients. All pumps used rapid analogue insulin. The mean number of basal rates (BR) used per patient was 2.1 ± 2.0; there was 1 BR in 22.0% of patients, 2 BR in 27.6%, 3 BR in 24.6% and 4–12 BR in 25.8%. The temporary BR function was used by 13.2% of patients. Boluses were triggered before meals by 64.2% of patients, during meals by 10.3%, after meals by 20.0% and as double boluses by 5.5%. Square-wave and combined boluses were used by 7.1 and 4.1% of patients, respectively. Sporting activities were reported by 57.5% of patients; time spent engaging in sports each week was more than 4 h in 7.5% of patients, 2–4 h in 11.4% and less than 2 h in 38.6%.

2.3.2. Infusion sets

The following Teflon infusion sets were used: Quick-Set®, 260 patients; Silhouette®, 22 patients; Sofset®, 14 patients and Tender®, nine patients. Metal needles were used by nine patients (including six using Polyfin® and three Rapid®) and not recorded in 25 patients. Mean duration of use per infusion set was 3.1 ± 0.9 days. The infusion set was disconnected regularly by 88.9% of patients, for a mean of 37 ± 8 min/day, for the following reasons: washing, 84%; sports, 15% and sexual intercourse, 33%. Only 11.1% of patients reported never disconnecting their infusion set. Over the past six months, infusion-set tolerance was good according to 80.2% of patients. Most of the infusion set-related adverse events were minor: irritation, 9.0%; transient inflammation, 6.0%; allergy to adhesive bandages, 4.2% and abscess requiring medical treatment, 2.4%. No abscesses requiring surgical drainage occurred. Local adverse events were influenced neither by the type of infusion set nor by the frequency of infusion-set changes.

2.3.3. Visual analogue scale scores for discomfort, acceptability and satisfaction

The mean VAS score for discomfort related to the catheter (0 = extreme discomfort to 10 = no discomfort) was 7.9 ± 2.2 cm and the mean VAS score for acceptability (0 = cannot accept the pump to 10 = fully accepts the pump) was 8.5 ± 1.9 cm. Patient satisfaction was high, with a mean VAS score (0 = very dissatisfied to 10 = very satisfied) of 8.2 ± 2.0 cm.

2.3.3.1. Factors associated with HbA1c levels

In the subpopulation of 339 patients treated with CSII for at least three months at inclusion into the registry, no associations were found between age, gender, living alone, years of education or body weight and HbA1c levels. HbA1c reduction varied significantly according to the reason for initiating CSII (P < 0.0001): larger reductions were seen in patients with insulin resistance (−2.91 ± 2.67%), poor glucose control (−1.80 ± 1.79%) or an irregular lifestyle (−1.44 ± 0.93%; P < 0.0001) than in those with unstable blood glucose levels (−0.81 ± 1.29%) or an inability to tolerate injections (−0.81 ± 1.54%). Pregnancy was associated with better glucose control (HbA1c, 6.65 ± 0.59 vs 7.82 ± 1.31%; P < 0.0001). HbA1c at registry inclusion showed positive correlations with HbA1c at CSII initiation (P < 0.0001) (Fig. 2) and with the number of ketotic episodes (P < 0.05), but was negatively correlated with the number of glucose self-determinations (P < 0.001 overall and P < 0.0001 for postprandial determinations), the number of hypoglycaemic episodes (P = 0.001) and the VAS patient-satisfaction score (P < 0.0001). HbA1c levels did not correlate with the frequency of infusion-set changes or with VAS scores for discomfort and acceptability. Patients who disconnected their pump regularly did not have significantly higher HbA1c levels (7.8 ± 1.39) compared with those who never disconnected their pump (7.6 ± 1.06%; P = 0.16). Also, HbA1c was not associated with the occurrence of infusion set-related events, use of transient BR function or use of square-wave or combined boluses. Patients who injected boluses before meals had slightly lower HbA1c levels (7.67 ± 1.28% vs 7.9 ± 1.4%, P = 0.06) than those who injected during meals (7.8 ± 1.4%) after meals (8.0 ± 1.3%) or as double boluses (8.5 ± 2.0%).

For the multivariate analysis, we entered potentially explanatory factors for HbA1c levels, excluding those that were consequences of HbA1c control (number of ketotic episodes and number of episodes of moderate and of severe hypoglycaemia). Factors significantly associated with HbA1c included the amount of physical activity, pregnancy, HbA1c level at CSII initiation and number of glucose self-determinations before meals and at night (Table 1).

2.3.3.2. Factors related to hypoglycaemia

Mild hypoglycaemic episodes were more common in patients with type 1 diabetes than with type 2 diabetes (2.9 ± 2.5/week vs 1.6 ± 2.6/week; P < 0.0001) and in women versus men (3.02 ± 2.85 vs 2.37 ± 2.07; P = 0.026), even after exclusion of pregnant patients. Use of the transient BR function was associated with a greater number of hypoglycaemic episodes (P = 0.047). Such episodes were also more common when the indication for CSII was pregnancy, an irregular lifestyle or blood
Table 1
Variables significantly associated with HbA1c in the multivariate analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Direction of HbA1c change</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical activity</td>
<td>Decrease</td>
<td>0.022</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Decrease</td>
<td>0.029</td>
</tr>
<tr>
<td>Higher HbA1c before CSII</td>
<td>Increase</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Larger number of premeal glucose self-determinations</td>
<td>Decrease</td>
<td>0.01</td>
</tr>
<tr>
<td>Larger number of nocturnal glucose self-determinations</td>
<td>Decrease</td>
<td>0.001</td>
</tr>
</tbody>
</table>

glucose instability (3.07 ± 3.14, 3.40 ± 2.88 and 2.83 ± 2.54, respectively) compared with an inability to tolerate insulin injections, poor glucose control and insulin resistance (2.57 ± 2.50, 2.54 ± 2.18 and 0.56 ± 1.01, respectively; P < 0.05). The number of episodes of moderate hypoglycaemia per week showed a positive correlation with the number of episodes of severe hypoglycaemia (P = 0.012), number of glucose self-determinations (P = 0.002) and BR number (P < 0.0001); there was a negative correlation with body weight, body mass index (BMI) (P < 0.0001) and HbA1c at CSII initiation (P = 0.036). The number of hypoglycaemic episodes did not correlate with age, diabetes duration, VAS scores for discomfort, acceptability or satisfaction, amount of physical activity, living alone, years of education, use of square-wave or combined boluses or use of boluses before, during or after meals. The only factors significantly and independently associated with the number of moderate hypoglycaemic episodes by multivariate analysis were BR number, female gender and HbA1c level (Table 2). HbA1c was negatively correlated with the number of moderate hypoglycaemic episodes (P < 0.001; Fig. 3), but not with the number of episodes of severe hypoglycaemia.

Table 2
Variables significantly associated with moderate hypoglycaemia in the multivariate analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Direction of moderate hypoglycaemia change</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal rate</td>
<td>Increase</td>
<td>0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>Increase</td>
<td>0.003</td>
</tr>
<tr>
<td>Higher HbA1c at last follow-up</td>
<td>Decrease</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
2.3.3. Results in type 2 diabetic patients. The 44 patients with type 2 diabetes were 57 ± 11.5 years of age (older than the other patients; \(P < 0.001\)) and 61% men; their BMI was 32.0 ± 6.1 kg/m² (higher than the other patients; \(P < 0.001\)). HbA1c decreased significantly between CSII initiation (9.42 ± 1.87%) and the study visit (7.63 ± 1.17%; \(P < 0.0001\)) and was not significantly different from the other patients’. However, the mean number of moderate hypoglycaemic episodes was lower in this subgroup (1.64 ± 2.45; \(P < 0.005\)); in addition, the number of severe hypoglycaemic episodes was 0.28 ± 0.91, affecting only four patients, with no episodes of acidoketosis. Mean VAS scores for discomfort related to the catheter and for satisfaction were similar to those of the other patients, while their mean VAS score for acceptability of the pump was better than that of the other patients (\(P < 0.005\)).

3. Discussion

Our pump registry was established as a tool for evaluating glucose control within the entire population of non-selected patients treated with CSII in our region. We were able to include 95.4% of this population (424 patients). In contrast, previous studies included selected patients who were subjected to closer monitoring than used in everyday practice. Under those study conditions, CSII was effective and safe [2–7]. However, little is known of the effects of CSII in patients who are not enrolled in studies.

Most of the patients in our registry had type 1 diabetes. However, patients with type 2 diabetes constituted 14% of our population, indicating that CSII was probably used as an alternative to MDI in these patients, as reported previously [8,9]. Poor glucose control was the main reason for CSII. In our study, HbA1c improved significantly with CSII—by more than 1% after a mean follow-up of 3.5 years (Fig. 1A). Similar decreases were found in meta-analyses [2,3,7], but have not been reported, to our knowledge, in observational studies. The largest HbA1c decreases occurred in the patients with the highest HbA1c levels before CSII, in keeping with the results of randomized studies (Fig. 2) [7]. This finding constitutes additional evidence that CSII is the treatment of choice in patients with poor glucose control. HbA1c levels were greater or equal to 9% in 40 patients (11% of the group with longstanding CSII use), who experienced a significant 0.9% improvement in their HbA1c levels as a result (Fig. 1B). This is similar to the 1% improvement found in the UK Prospective Diabetes Study to be associated with a 37% reduction in long-term diabetes complications [10]. Although target glucose levels may not be achieved in all patients, CSII provides benefits to patients whose glucose control is inadequate under an MDI regimen.

Lower HbA1c levels were associated with higher numbers of moderate hypoglycaemic episodes (Fig. 3), but not with severe
hypoglycaemia, in contradiction to results from the Diabetes Control and Complications Trial [1]. Thus, in some patients, CSII combined with appropriate patient education ensured excellent glucose control without increasing the risk of severe hypoglycaemia. Similar benefits have been reported with flexible intensive insulin therapy [11]. However, a subset of patients using CSII experiences severe hypoglycaemia regardless of HbA1c level. These patients may be candidates for alternative treatment methods such as insulin-pump implantation [12] or islet transplantation [13].

We obtained valuable data on the types of insulin-pumps used by patients in everyday practice. The BR number varied widely, from 1 to 12, and was not associated with glucose control. Higher BR numbers were significantly associated with a greater number of moderate hypoglycaemic episodes. There is clearly a need for recommendations concerning the optimal BR number. Studies involving continuous glucose monitoring can be expected to lead to a consensus on this issue. Patients in our registry were instructed to administer insulin boluses immediately before meals. However, 36% of patients reported administering boluses during or after meals; although these patients did not experience more hypoglycaemic episodes, they did show a trend (P = 0.06) towards higher HbA1c levels, in keeping with the 0.2% higher HbA1c noted in patients who injected Glulisine 20 min after meals compared with those who injected before meals [14]. Thus, although insulin is best given before meals, injecting during or after meals of unknown carbohydrate content has only minor effects on glucose control. Few patients used square-wave or combined boluses. Infusion-set-related adverse events were uncommon and minor, mostly consisting of skin irritation. The time interval between infusion-set changes was not correlated with adverse events. Patients changed their infusion sets about every three days, in accordance with recommendations. The time interval between changes also did not correlate with HbA1c, suggesting that less frequent changes may be a valid option with new-generation infusion sets. A randomized controlled study is needed to evaluate this possibility.

We used VAS scores to assess CSII discomfort, acceptability and satisfaction. Discomfort and poor acceptability were uncommon and unrelated to HbA1c levels. Patient satisfaction, in contrast, correlated with HbA1c, suggesting that perceived good glucose control may improve patients’ lifestyle activities and quality of life.

The results in type 2 diabetes patients confirm that, in real life, CSII is feasible, effective and even better tolerated than type 1 diabetes in younger patients [9].

In conclusion, our comprehensive regional registry provides valuable information that establishes the effectiveness of CSII in everyday life, while also highlighting the risks of severe hypoglycaemia and ketosis. The information provided by the registry on how patients use their insulin-pumps will help diabetologists to improve patient-training programmes and follow-up. There is room for improving the modalities of insulin-pump use. After one year, the data in the registry will be evaluated to determine whether improvements have occurred compared with the present situation.

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Appendix A

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