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Continuous glucose monitoring reduces both hypoglycaemia and HbA_{1c} in hypoglycaemia-prone type 1 diabetic patients treated with a portable pump

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Abstract

Aim. - This study aimed to assess the effectiveness of continuous glucose monitoring (CGM) for glucose control in type 1 diabetic patients treated by continuous subcutaneous insulin infusion (CSII) and presenting with frequent hypoglycaemic episodes.

Methods. - Thirteen patients with type 1 diabetes (diabetes duration: 25 ± 15 years; CSII duration: 5.5 ± 7.0 years), with more than six recorded capillary blood glucose (CBG) values < 60 mg/dL, according to their metres for the past 14 days, were offered the permanent use of a CGM device (Guardian RT®, Medtronic) plus ongoing self-monitoring of blood glucose (SMBG) for 12 weeks, followed by a 12-week crossover period of SMBG only, or *vice versa*. Glucose control, determined by recorded 14-day CBG values < 60 mg/dL and HbA_{1c} levels, and quality of life according to the Diabetes Quality of Life (DQOL) questionnaire, were assessed at baseline, and after 12- and 24-week follow-ups.

Results. - Four patients withdrew from the study during the first period (of whom three were using CGM). In the nine study completers, the number of low CBG values decreased significantly from 13.9 ± 9.2 to 7.6 ± 6.8 (P = 0.011) when patients used CGM, in either the initial or final trial period, while a decrease in $HbAi_c$ from 8.3 ± 0.7 to 7.7 ± 0.6% (P = 0.049) was also observed, in contrast to the absence of any significant differences during the SMBG-only period. DQOL scores were also essentially unaffected.

Conclusion. - This pilot observational study supports the hypothesis that CGM use can significantly improve overall glucose control while reducing hypoglycaemic episodes in hypoglycaemia-prone type 1 diabetic patients treated by CSII.

Résumé

L'apport d'une mesure continue du glucose réduit le taux d'HbA_{1c} et la fréquence des hypoglycémies chez des patients diabétiques de type 1 traités par pompe portable à insuline et à risque hypoglycémique.

Objectif. - Étudier l'efficacité d'un système de mesure continue du glucose sur le contrôle glycémique de patients diabétiques de type 1 traités par pompe portable à insuline et présentant des hypoglycémies fréquentes.

Méthodes. - Treize patients diabétiques de type 1 (durée du diabète : 25 ± 15 années ; durée du traitement par pompe : 5,5 ± 7,0 années), présentant plus de six glycémies capillaires inférieures à 60 mg/dl enregistrées dans leur lecteur à mémoire durant les 14 derniers jours, ont participé à une étude observationnelle. Cette dernière comprenait deux périodes de 12 semaines en ordre croisé, avec soit le recours complémentaire à un système de monitoring du glucose (Guardian RT®, Medtronic), soit seulement lapoursuite de l'autosurveillance glycémique habituelle. Le contrôle glycémique, évalué sur la base du nombre de glycémies capillaires inférieures à 60 mg/dl au cours des 14 derniers jours et du taux d'HbA_{1c}, et la qualité de vie ont été analysés à l'inclusion, après 12 semaines et après 24 semaines.

Résultats. - Quatre patients se sont retirés de l'essai durant la première période (dont trois alors qu'ils étaient sous Guardian RT®). Chez les neuf patients ayant achevé l'étude, le nombre de valeurs glycémiques basses a diminué de 13,9 ± 9,2 à 7,6 ± 6,8 (p = 0,011) lorsque les patients utilisaient le Guardian RT®, que ce soit en période 1 ou en période 2, tout en obtenant une réduction du taux d'HbA_{1c} de 8,3 ± 0,7 à 7,7 ± 0,6 % (p = 0,049), alors qu'il

n'y avait pas de différences significatives durant la période sous simple autosurveillance glycémique habituelle. La qualité de vie n'a pas paru affectée.

Conclusions. - Cette étude pilote supporte l'hypothèse selon laquelle la mesure continue du glucose peut améliorer le contrôle glycémique tout en diminuant la fréquence des hypoglycémies chez des patients diabétiques de type 1 à risque hypoglycémique sous traitement par pompe portable à insuline.

Keywords : Type 1 diabetes ; Hypoglycaemia ; Continuous glucose monitoring ; Insulin pump ; Quality of life

Mots clés : Diabète de type 1 ; Hypoglycémie ; Enregistrement continu du glucose ; Pompe à insuline ; Qualité de vie

1. Introduction

The current goals of glucose control in patients with type 1 diabetes mellitus (T1DM) include glycated haemoglobin (HbA_{1c}) < 7% together with the lowest possible rate of hypoglycaemia. Besides impaired quality of life (QOL), frequent mild-to-moderate hypoglycaemic episodes have also been associated with an increased risk of severe hypoglycaemia because of a lack of hypoglycaemia awareness [1]. Continuous subcutaneous insulin infusion (CSII) can lead to lower HbA_{1c} levels than with multiple daily insulin injections in T1DM patients [2,3], with a significant reduction in severe hypoglycaemic episodes [4]. However, a subset of CSII-treated patients still experiences frequent hypoglycaemic events in everyday life [4,5].

Nevertheless, the increasing availability of continuous glucose monitoring (CGM) is helpful in detecting hyper- and hypoglycaemic deviations that might otherwise go unrecognized with self-monitoring of blood glucose (SMBG) only [6]. Until now, the demonstrated benefits of CGM have focused on reducing HbA_{1c} in patients who were far from achieving their targeted HbA_{1c} levels [7,8], while outcomes of CGM use on the occurrence of hypoglycaemia have been poorly investigated and for short time-periods only [9]. For this reason, the present study aimed to assess glucose control with 12-week CGM use compared with the usual SMBG in hypoglycaemia-prone T1DM patients treated by CSII. By design, the selected study population consisted of T1DM patients without severe hypoglycaemia or brittle diabetes but, instead, had frequent mild biochemical hypoglycaemia [10]. It is known that repeatedly low glucose levels detected by SMBG may reflect prolonged periods of asymptomatic hypoglycaemia, which may be deleterious for cognitive function and lead to arrhythmias [11].

2. Methods

The present study included 13 adult T1DM patients - treated by CSII for at least 1 year, with at least four quarterly visits a year to optimalize insulin therapy - who also had more than six recorded capillary blood glucose (CBG) values < 60 mg/dL, according to their metres, within the last 14 days prior to a routine visit to our centre. All of the included patients provided their written informed consent to participate in the observational study, which had been accepted by our institutional ethics board.

The study included two consecutive 12-week periods according to a crossover design in which the sequential order was randomly determined. During the CGM period, patients were offered the permanent use of a CGM device (Guardian RT®, Medtronic, Northridge, CA, USA), which visually displayed their estimated blood glucose levels at 5-min intervals, as well as the usual SMBG. During the SMBG-only period, no CGM was performed. The primary study endpoint was the number of recorded CBG values < 60 mg/dL in the metre memory for the last 14 days of each 12-week period. Secondary endpoints included HbA_{1c} levels and QOL scores at the end of each study period.

During both periods, all patients performed the usual SMBG, using their own memory metres calibrated against the standard glucose solution at each visit. All patients also had to review the guidelines for adapting their pump basal rates and bolus insulin doses according to SMBG data at study entry. However, no algorithm for the use of either CGM data or SMBG values was provided, thus replicating real-life conditions.

The Guardian RT device estimates blood glucose values *via* a subcutaneously inserted glucose-oxidase-based sensor that generates a continuous signal according to interstitial glucose levels [9]. Blood glucose estimates presented on the device screen correspond to the average glucose level over the past 5-min period, based on

prospective calibration of the sensor signal against twice-daily capillary blood glucose (CBG) measurements. A specific training period, lasting about 2h, for CGM self-management was allocated for each patient before the period of CGM use. Blood glucose alert thresholds were initially set for all study patients at 80 mg/dL for hypoglycaemia and 240 mg/dL for hyperglycaemia, taking into account an estimated delay between actual and displayed blood glucose values [5]. However, these settings could be readjusted, if necessary, by the patient's physician on day 14 of the CGM period.

Study visits were scheduled on day 14 of each study period to check each patient's management of the SMBG data and, during the CGM period, of the CGM device and data, at the 12-week crossover and at 24 weeks (end of the study). CBG measurements over the last 14 days prior to the visits at baseline, and at 12 and 24 weeks, were downloaded from the metre memory to compute the number of values < 60 mg/dL. HbA_{1c} measurements and QOL, as determined by a validated questionnaire [12,13], were also assessed at these time points.

Baseline patients' characteristics and the results for continuous variables were expressed as means ± SD. A non-parametric analysis of variance (ANOVA) method was used to assess changes in the studied parameters, and the Mann-Whitney test was used to evaluate the presence of any period effect. Data were analyzed using Statistica v7.1 (StatSoft® France 2005) software, and statistical significance was set at the 5% level.

3. Results

Of the 13 enrolled patients, seven started the study with CGM and six with SMBG only. Four patients withdrew from the study within the first 2 weeks. The three patients who dropped out while using CGM did so because of skin reactions at sensor-insertion sites, an inability to manage CGM data and the discomfort of wearing the CGM system during sports activities, respectively. The single patient who withdrew from the study during the SMBG-only period wished to have an implantable insulin-pump system because of severe blood glucose variability despite CSII. No statistically significant differences in baseline characteristics between the nine patients who completed the study and the 13 who were initially randomized were found in terms of age (47.4 ± 10.0 *vs* 47.1 ± 11.0 years, respectively), diabetes duration (25 ± 15 *vs* 26 ± 16 years, respectively), CSII duration (5.5 ±7.0 *vs* 5.6 ±7.0 years, respectively), baseline HbA_{1c} (8.3 ± 0.4% *vs* 8.2 ± 0.4%, respectively), number of capillary glucose tests in the 14 days prior to randomization (87 ± 35 *vs* 91 ± 39, respectively) and number of CBG values < 60 mg/dL during the last 14 days of each study period (15.0 ± 8.6 *vs* 16.0 ± 8.9, respectively).

CGM use and sensor insertions were both well tolerated by the nine study completers. Compliance with the recommended permanent use of the CGM device and sensor changes every 3 days were close to 100%, according to the checked sensor-use count and analysis of the recordings for the last 2 weeks prior to the control visit. No ketoacidosis or severe hypoglycaemia was seen at any time during the study.

Whereas all of the study patients had more than six recorded CBG values < 60 mg/dL in their metre memory for the 14 days before entering the study (baseline), six of the nine completers had six or less such CBG values for the last 14 days of CGM use (two of four patients who started with CGM use, and four of five patients who ended with CGM use); in contrast, only one patient achieved such a result during the SMBG-only period (in the starting period in this case). No statistically significant period effect could be found. The number of low CBG values decreased significantly when patients used CGM, whereas there was no significant difference during the SMBG-only period (Table 1). The number of patients with less than six hypoglycaemic values for the last 14 days rose from 0 (baseline) to six with CGM, and from 0 to one with SMBG only. No influence of previous CSII duration was noted. Direct comparison of all three conditions showed 15.3 ± 8.6 CBG values < 60 mg/dL (out of 87 ± 35 measurements) for the last 14 days at baseline, 7.6 ± 6.8 values < 60 mg/dL (out of 79 ± 46 measurements) for the last 14 days of CGM (P = 0.0076 *vs* baseline) and 11.1 ± 4.5 values < 60 mg/dL (out of 81 ± 39 measurements) for the last 14 days of SMBG only (not significant *vs* baseline).

HbA_{1c} levels decreased significantly with CGM use, but not with SMBG only (Table 1). In addition, the basal rate of insulin delivery showed no significant changes between the two study periods from baseline. However, most patients reported making corrections with insulin when CGM indicated hyperglycaemia, a behaviour that most likely played a role in the improvement of HbA_{1c} levels seen during the CGM period.

Furthermore, diabetes QOL scores were not significantly different at the end of each study period *vs* baseline in terms of global scores (Table 1), as well as those for each specific item under study (satisfaction, personal impact, social and vocational worry, diabetes worry and well-being; data not shown).

Table 1 *Glucose control and Diabetes Quality of Life (DQOL) total score for the nine study completers with continuous glucose monitoring (CGM) and self-monitoring of blood glucose (SMBG).*

	Before CGM	With CGM	*P*	Mean difference [95% CI]
HbA_{1c} (%)	8.3 ± 0.7	7.7 ± 0.6	0.049	0.53 ± 0.66 [0.02-1.0]
Number of hypos[a]	13.9 ± 9.2	7.6 ± 6.8	0.011	6.2 ± 5.2 [2.2-10.2]
Patients without hypos[a]	0/9[c]	6/9[d]	0.05[f]	
DQOL total score[b]	64.7 ± 11.0	67.0 ± 7.6	0.32	-2.3 ± 5.3 [-6.4-1.7]
	Before SMBG only	With SMBG only	*P*	Mean difference [95% CI]
HbA_{1c} (%)	7.9 ± 0.5	8.0 ± 0.8	0.48	-0.09 ± 0.5 [-0.48-0.30]
Number of hypos[a]	11.8 ± 7.1	11.1 ± 4.5	0.55	0.67 ± 6.9 [-4.7-6.0]
Patients without hypos[a]	0/9[c]	1/9[e]	NS[f]	
DQOL total score[b]	65.1 ± 11.0	64.4 ± 10.5	0.48	0.7 ± 4.1 [-2.5-3.8]

Hypos: hypoglycaemic episodes; NS: not significant.
[a] Capillary blood glucose values < 60 mg/dL during the last 14 days.
[b] On a scale of 0-100, the higher the DQOL score, the better the quality of life.
[c] Assessed at baseline.
[d] Two of four patients who started the study with CGM, and four of five who ended the study with CGM (no statistically significant period effect).
[e] One patient who started the study with SMBG only.
[f] Chi^2 test *vs* baseline.

4. Discussion

Our study demonstrates the benefits of permanent CGM for 12 weeks with the reduction of low blood glucose values in a subset of T1DM patients prone to hypoglycaemia during CSII. Moreover, the reduction of hypoglycaemic values while using CGM was associated with improvement of HbA_{1c} levels, an unusual finding in patients with T1DM for whom the intensification of insulin therapy to lower HbA_{1c} levels is generally associated with a higher rate of hypoglycaemic episodes [1]. The importance of glucose variability and the positive effect of CSII have previously been emphasized in this regard [14].

However, the sustained benefits of CGM use have been controversial in clinical practice so far [8,15]. Permanent use of the Guardian RT device for 3 months significantly improved HbA_{1c} levels compared with SMBG, while intermittent CGM use showed no significant benefit [6]. The recent Juvenile Diabetes Research Foundation (JDRF) trial reported that CGM for 6 months led to significant HbA_{1c} improvement *vs* SMBG use only in young patients who showed good compliance with sensor use [16], although the incidence of severe or biochemical hypoglycaemic events was not significantly altered. In the recent French multicentre REAL Trend study, CGM-enabled insulin-pump therapy improved glycaemia more than conventional pump therapy during the first 6 months of pump use in T1DM patients who wore CGM sensors at least 70% of the time, but had no impact on hypoglycaemia [17]. However, in none of these studies was patient enrolment based on a previous high incidence of documented biochemical hypoglycaemia.

In contrast, in the present pilot study, T1DM patients were selected because of frequently detected low glucose levels (six or more values < 60 mg/dL within the past 14 days). This rate of biochemical hypoglycaemia was considerably higher than that reported in other studies, such as the recent report by the UK Hypoglycaemia Study Group comparing the frequency of biochemical hypoglycaemia in adults with T1DM with and without impaired awareness of hypoglycaemia [18]. The permanent use of CGM in our present patients treated by CSII and presenting with such a high incidence of hypoglycaemia was associated with significant reductions in both the incidence of hypoglycaemic episodes and HbA_{1c} levels. In spite of intensive SMBG use and recently reinforced training on adaptation of insulin delivery, no significant reduction of hypoglycaemic values was obtained during the study period without CGM. Being informed of the potential risk of hypoglycaemia *via* the CGM system most likely helped these patients to anticipate the need for countermeasures to avoid the occurrence of hypoglycaemia [5]. The concomitant reduction in HbA_{1c} levels may also indicate the patients' greater self-confidence in adapting insulin doses to reduce hyperglycaemia safely because of the CGM information.

Nevertheless, the currently available CGM devices still need to be improved and made easier to use in everyday life, as revealed by the rather high initial dropout rate in our study. The lack of improvement in QOL despite the better glucose control with CGM use, including less-frequent hypoglycaemic episodes, may be related to the constraints of wearing and managing the CGM system, although the patients who completed the study all

showed excellent compliance with sensor use. In a recent study, users of the integrated real-time CGM/CSII system reported more treatment benefits, greater treatment satisfaction and better QOL than SMBG + CSII users [12].

In conclusion, diabetic patients who remain prone to hypoglycaemia in spite of CSII treatment appear to be good candidates for CGM use, and such patients warrant further investigation in larger-scale trials with similar features to confirm our present findings.

Conflict of interest statement

No relevant conflict of interest to declare.

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