Short-term use of continuous glucose monitoring system adds to glycemic control in young type 1 diabetes mellitus patients in the long run: A clinical trial

Kratkotrajna primjena kontinuiranog mjerenja glikemije poboljšava metaboličku kontrolu kod djece i adolescenata sa dijabetesom melitusom tip 1 na duži period: kliničko ispitivanje

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Abstract

Background/Aim. Balancing strict glycemic control with setting realistic goals for each individual child and family can optimize growth, ensure normal pubertal development and emotional maturation, and control long-term complications in children with type 1 diabetes (T1DM). The aim of this study was to evaluate the efficacy of short-term continuous glucose monitoring system (CGMS) application in improvement of glycemic control in pediatric type 1 diabetes mellitus (T1DM) patients. Methods. A total of 80 pediatric T1DM patients were randomly assigned into the experimental and the control group. The experimental group wore CGMS sensor for 72 hours at the beginning of the study. Self-monitored blood glucose (SMBG) levels and hemoglobin A1c (HbA1c) levels were obtained for both groups at baseline, and at 3 and 6 months. Results. There was a significant improvement in HbA1c (p < 0.001), in both the experimental and the control group, without a significant difference between the groups. Nevertheless, after 6 months the improvement of mean glycemia was noticed only in the experimental group. This finding was accompanied with a decrease in the number of hypoglycemic events and no increase in the number of hyperglycemic events in the experimental group. Conclusions. The results suggest that the CGMS can be considered as a valuable tool in treating pediatric T1DM patients, however further research is needed to more accurately estimate to what extent, if any, it outperforms intensive self-monitoring of blood glucose.

Key words: diabetes mellitus, type 1; adolescent; child; child, preschool; blood glucose self-monitoring.

Apstrakt

Uvod/Cilj. Balansiranjem stroge glikemijske kontrole sa postavljanjem realnih ciljeva za svako pojedinačno dete i porodicu može se optimizirati rast, odrediti normalan razvoj u pubertetu, kao i emocionalno sazrevanje i dugoročna kontrola kompleksa kod dece sa dijabetesom tip 1 (T1DM). Cilj ove studije bio je da se procijeni efikasnost metoda kontinuiranog supkutanog mjerenja glikemije u postizanju bolje glikemijske kontrole kod dece i adolescenata sa dijabetesom melitusom tip 1. Metode. Ukupno 80 djece sa dijabetesom melitusom tip 1 slučajnim odabirom određeno je u eksperimentalnu ili kontrolnu grupu. Ispitanici u eksperimentalnoj grupi nosili su aparat za kontinuirano praćenje glikemije (CGMS aparat) 72 sata na početku studije. Za ispitanike iz obje grupe evidentirani su podaci samokontrolisane glikemije (SMBG) i hemoglobina A1c (HbA1c) na početku studije, nakon tri i nakon šest mjeseci. Rezultati. Dobijeno je značajno poboljšanje koncentracije HbA1c na tri i šest mjeseci i u eksperimentalnoj i kontrolnoj grupi (p < 0,001), bez značajne razlike među grupama. Nasuprot tome, značajno smanjenje srednje glikemije nakon šest mjeseci zabilježeno je samo u eksperimentalnoj grupi. Nadalje, u eksperimentalnoj grupi doslo je i do smanjenje broja hipoglikemijskih događaja, a, pri tom, nije evidentiran porast broja hypoglikemijskih događaja. Zaključak. Rezultati studije sugeriraju da sistem kontinuiranog supkutanog praćenja glikemije može biti korisno sredstvo metaboličke kontrole kod dece sa dijabetesom melitusom tip 1, ali neophodna su dodatna istraživanja kako bi se preciznije utvrdilo u kojoj mjeri, ako je to uopšte slučaj, ovaj metod, u terapeutskom smislu, nadmašuje intenzivno samokontrolisanje glikemije.
Introduction

Balancing strict glycemic control with setting realistic goals for each individual child and family can optimize growth, ensure normal pubertal development and emotional maturation, and control long term complications in children with type 1 diabetes (T1DM). The goal of the usual intensive therapy is to maintain near-normal glycemia, normalize hemoglobin A1c (HbA1c), control postprandial glycemic excursion and decrease the number of hypoglycemic events. Although very useful, multiple, four daily blood glucose measurements are still insufficient to provide and predict all relevant glycemic fluctuations. A newer method of continuous glucose monitoring (CGMS) seems to address the issue.

The CGMS provides the maximal amount of data about glycemic profile during activities of daily living, including physical activity, work, meals, and sleep. Thus, continuous monitoring have a great potential value to improve glycemic control and decrease the number of hypoglycemic events. In addition, the CGMS has shown that hypoglycemia is underdiagnosed, underscored or else tolerated by patients in the experimental group. There was no evidence of infection or inflammation at the insertion site of the sensor. The CGMS data were analyzed using the Medtronic-MiniMed Solution Software version 3.0B (Medtronic). In both groups, the patients underwent 3 days of self-monitoring of blood glucose using an Accucheck glucometer (Roche), before and after each main meal, at bedtime, and during the night at 2 a.m. and 5 a.m. The postmeal measurements were taken within 2 hours after the preprandial measurements. Four of the SMBG tests were entered into the CGMS monitor for calibration. Sensor insertion and CGMS training as well as SMBG training were done in hospital, after which the patients returned home to their usual insulin therapy, diet and activity. Hemoglobin A1C (HbA1c) level was measured using the DCA 2000 (Bayer, Tarrytown, NY; non-diabetic range 4.3%–6.3%) at the beginning of the study and after 3 and 6 months.

Results

As can be seen from Tables 1 and 2, the experimental and control groups were similar with regard to their average body mass indexes, sex distribution, and baseline measures of HbA1c. Yet, the experimental group included on average group of the patients and families were instructed by the same investigator in the use of the CGMS device and they were asked to enter at least four daily blood glucose measures obtained with a personal glucometer into the instrument for the calibration purpose. They also entered all data regarding insulin administration, meals taken, exercise and other relevant events (e.g. hypoglycemic symptoms). The CGMS (Medtronic MiniMed, Northridge, CA) was applied for 72 hours including three overnight profiles and was well tolerated by patients in the experimental group. There was no evidence of infection or inflammation at the insertion site of the sensor. The CGMS data were analyzed using the Medtronic-MiniMed Solution Software version 3.0B (Medtronic). In both groups, the patients underwent 3 days of nine-point self-monitoring of blood glucose using an Accu-check glucometer (Roche), before and after each main meal, at bedtime, and during the night at 2 a.m. and 5 a.m. The postmeal measurements were taken within 2 hours after the preprandial measurements. Four of the SMBG tests were entered into the CGMS monitor for calibration. Sensor insertion and CGMS training as well as SMBG training were done in hospital, after which the patients returned home to their usual insulin therapy, diet and activity. Hemoglobin A1C (HbA1c) level was measured using the DCA 2000 (Bayer, Tarrytown, NY; non-diabetic range 4.3%–6.3%) at the beginning of the study and after 3 and 6 months. In the experimental group, CGMS data were collected and reviewed and therapeutic decisions during the first three months were made based on both CGMS and SMBG data, whereas hyperglycemia was defined as capillary blood glucose (CBG) level lower than 3.5 mmol/L, whereas hyperglycemia was defined as CBG level higher than 10.0 mmol/L.

Raw data were summarized and expressed as counts (categorical data) or means ± standard deviations (numeric data). Bivariate relationships were estimated with Pearson's linear correlation coefficients. Group differences were assessed with the Fisher exact tests, Wilcoxon-Mann-Whitney tests (exact probabilities), Wilcoxon signed-ranks tests (exact probabilities), and Student's t-tests (for independent and paired samples) corrected for unequal variances, where needed. The level of statistical significance was set at \( p < 0.05 \) (all tests two-tailed). The Statistical Package for Social Sciences (SPSS, Chicago) was used for all statistical analyses.
older children with longer diabetes duration. Furthermore, both the baseline average insulin dose, as well as the initial average glucose levels, were significantly higher in the experimental group (Tables 1 and 2). Interestingly, in neither group did the average insulin dose change noticeably during the course of the study (Table 1), despite the modifications of therapy in individual cases (Table 3 presents the most relevant modifications).

Median duration of sensor wear was 72 h in the experimental group with the average number of CGMS readings per subject equaling 864. The mean plasma glucose level measured by SMBG (10.6 ± 1.9 mmol/L) did not differ significantly from that measured by CGMS (10.6 ± 2.3 mmol/L) \((p = 0.765)\). These two measures correlated highly and statistically significantly \((r = 0.86, p < 0.001)\). In contrast, linear correlation between HbA1c and mean glycemia

| Characteristics | Baseline | 3 months | 6 months |
|-----------------|----------|----------|----------|
| Number of patients | 40 | | |
| Experimental group | 22 (55.0) | 0.655 |
| Female (n, %) | 0.655 |
| Age (M ± SD) (yrs) | 13.7 ± 3.3 |
| Experimental group | 6.3 ± 4.0 |
| Diabetes duration (yrs) | 6.3 ± 4.0 |
| Experimental group | 0.85 ± 0.23 |
| Insulin (dose/kg) (M ± SD) | 0.85 ± 0.23 |
| Experimental group | 0.72 ± 0.18 |
| BMI (kg/m²) (M ± SD) | 19.1 ± 2.7 |
| Experimental group | 0.85 ± 0.22 |
| Experimental group | 0.005 |
| Control group | 0.76 ± 0.22 |
| Control group | 18.5 ± 2.6 |
| Experimental group | 0.163 |
| Control group | 0.76 ± 0.23 |
| p | 0.002 |

\(\Delta (1-2)\) – difference in average levels between baseline and 3-month measurement;

\(\Delta (1-3)\) – difference in average levels between baseline and 6-month measurement

| Interventions | Experimental group | Control group |
|---------------|--------------------|---------------|
| Long-acting insulin change | 25 (62.5) | 20 (50.0) |
| increase | 22 (55.0) | 17 (42.5) |
| decrease | 3 (7.5) | 3 (7.5) |
| Rapid/short-acting insulin change | 17 (42.5) | 12 (30.0) |
| increase | 15 (37.5) | 9 (22.5) |
| decrease | 2 (5.0) | 3 (7.5) |
| Carbohydrate intake changes | 15 (37.5) | 9 (22.5) |
| Increase of physical activity | 8 (20.0) | 9 (22.5) |

\*The results are presented as frequencies and percentages (given in parentheses)
measured by SMBG was small in magnitude, but significant ($r = 0.14, p = 0.032$).

At the baseline, the mean hemoglobin A1c value in the experimental group was $10.0 \pm 1.6\%$, whereas it was insignificantly higher in the control group $10.2 \pm 2.0\%$. A significant improvement in HbA1c was observed in both groups after 3 and 6 months ($p < 0.001$) (Table 2). However, the degree of improvement in HbA1c was not statistically significantly different between the two groups, neither at 3 months ($p = 0.604$), nor after 6 months ($p = 0.705$).

Mean glycemia (self-monitored, both groups) were significantly improved in the experimental group after 3 and 6 months (both $p = 0.01$) (Table 2). In the control group, there was an initial decrease in mean glycemia after 3 months, which was not significant ($p = 0.117$), but after 6 months mean glycemia reversed back almost to the baseline level ($p = 0.813$, compared to the baseline). No significant difference in mean glycemia between two groups was found after 3 months ($p = 0.256$); nonetheless, mean glycemia showed to be significantly better controlled in the experimental group than in the control group after 6 months ($p = 0.002$). Table 2 shows a continuous trend of improvement of mean glycemia in the experimental group, contrasted to the control group’s only temporary improvement.

A statistically significant decrease in the number of hyperglycemic events per patient per day was observed in the experimental group after 6 months ($p = 0.022$) (Table 4). Also, there was a decrease in the number of hypoglycemic events after 6 months, although it did not reach a statistically significant level ($p = 0.223$) (Table 4). In the control group there was an improvement in the average number of hypoglycemia per patient both after 3 and 6 months compared to the baseline, albeit it was not statistically significant (Table 4). A significant decrease in the average number of hyperglycemia per patient was found in the control group after 3 months ($p = 0.017$), but not after 6 months ($p = 0.828$) (Table 4).

Discussion

The results of this six-month long study suggest that even a short-term use of the CGMS method influences therapy decisions and subsequently leads to the improvement of metabolic control in young T1DM patients in the long run; still, the advantage over the intensive classic method (intensive self-monitoring) is not straightforward. Specifically, the improvement in average HbA1c levels was observed in both groups and the difference between them was neither clinically nor statistically significant (1.4% drop in the experimental and 1.3% in the control group). Yet, other clinically important outcomes measured (namely mean glucose levels, number of hypoglycemic and hyperglycemic events) showed higher treatment effects in the experimental group in the long run. We propose some explanations for such ambiguous results.

Firstly, all our participants had relatively high average HbA1c levels ($\geq 8\%$), with one-third of them having values over $10\%$ at some point of the study. The earlier-mentioned low correlation between mean glycemia and HbA1c can be thus ascribed to the restricted range of the scores; the effect of which is a reduced correlation when compared to its magnitude observed in whole population. Therefore, these two measures cannot be seen as interchangeable in assessing glycemic states in our sample. Furthermore, due to the relative protractenedness of HbA1c (HbA1c known to be influenced by glycemic levels of up to four months before the measurement)$^{12,13}$ we are inclined to believe that mean glucose levels are more appropriate measures in detecting fine and more recent changes in glycemic levels in a highly event-dynamic sample as was ours. In other words, it is possible that HbA1c was not sensitive enough to detect the changes in the control group in the last three months of the trial, and, as a result, we obtained no statistically significant differences with regard to HbA1c, which was in contrast to other relevant findings.

We also suspect that short-term improvements in the control group in the first three months could be caused by the so-called “experimental effect” which the study had on the participants. In particular, it seems reasonable that “reactivity of measurement”$^{14}$ phenomenon had taken place; namely, thanks to the frequent intensive SMBG measurements at the baseline the participants might have changed their health-related behaviors, but the benefits of it faded out in the course of time. On the contrary, the group receiving treatment and accompanying advice on the basis of their CGMS measures persisted in showing improvements in all outcomes (quite the opposite to what Yates et al.$^{15}$ found) throughout

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| Table 4 |
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| Period of the study | Hypoglycemia | Hyperglycemia |
| --- | --- | --- |
| Experimental group | Control group | $p^*$ | Experimental group | Control group | $p^*$ |
| Baseline | $0.8 \pm 0.7$ | $0.7 \pm 1.4$ | 0.015 | $4.3 \pm 1.7$ | $3.6 \pm 2.1$ | 0.266 |
| 3 months | $0.6 \pm 0.6$ | $0.5 \pm 0.6$ | 0.429 | $3.6 \pm 2.1$ | $3.0 \pm 1.9$ | 0.910 |
| 6 months | $0.6 \pm 0.6$ | $0.6 \pm 1.4$ | 0.468 | $3.2 \pm 1.6$ | $3.6 \pm 2.3$ | 0.115 |
| $p \Delta (1-2)^{12}$ | 0.180 | 0.715 | 0.089 | 0.017 |
| $p \Delta (1-3)^{12}$ | 0.223 | 0.175 | 0.022 | 0.828 |

*The results are presented as mean ± standard deviation obtained from 27 measures per visit (9 capillary glycemic tests × 3 days) per individual. Hypoglycemia defined as blood glucose < 3.5 mmol/L; hyperglycemia as blood glucose > 10.0 mmol/L. *Wilcoxon-Mann-Whitney test (between-subjects effects) controlled for baseline differences. ‡Wilcoxon signed-ranks test (within-subjects effects) examining changes from the baseline levels. 

$1-2 = \text{difference in average number of events per day between baseline and 3-month measurement;}$  
$1-3 = \text{difference in average number of events per day between baseline and 6-month measurement}$. 

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the study, which might indicate profound changes in treatment adherence.

Indeed, further empirical investigation is required to prove the aforementioned hypothesis, even though psychological effects on diabetes treatment adherence when monitoring blood glucose levels with memory-equipped devices have already been discussed. Although the experts emphasize the potential benefits of those devices, some concern was over the possible information overload for the patients. With regard to this, we believe the overload would be less of an issue when the CGMS is used for a short-term only and under medical supervision, as was the case in our study. It must be stated, however, that our intention was not to imply that three-day use would be its suggested use; rather we merely tested whether short-term application of the CGMS could be of any value for clinical practice.

Conclusion

A significant reduction of mean glycemia and hypoglycemic events compared to the control group, accompanied with the observed reduction of HbA1c levels and the number of hypoglycemic events does lead us to a conclusion that the CGMS is a valuable add-on in the control of type 1 diabetes in young patients, even when used for such a brief period. It represents a newer methodology that seems to be better accepted by both younger patients and their parents since it produces comprehensible graphic-imaging of glycemia dynamics, which at least in theory, should lead to better patient’s and parents’ compliance with the therapy. From the practitioner’s perspective, we found that the CGMS offers more information and allow for better decisions in the course of therapy, especially with regard to the insulin administration (dosage and timing) which plays a crucial role in glycemic control. Still, more research is needed in order to determine optimal parameters of CGMS use to exploit it in the most effective way. Lastly, it seems that intensified (e.g. 9-point) self-monitoring of blood glucose has its benefits as well and that at this stage of research it can be perceived as a second-choice alternative to the CGMS, especially in economically challenged countries, such as Bosnia & Herzegovina, where affording continuous glucose measuring devices could still represent an issue.

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Received on February 10, 2010.
Revised on June 28, 2010.
Accepted on July 27, 2010.