

Efficacy of Continuous Glucose Monitoring System to Detect Unrecognized Hypoglycemia in Children and Adolescents With Type 1 Diabetes

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ABSTRACT

This retrospective study assessed 17 DM1 pediatric patients (15.76 ± 4.5 years) submitted to 72h continuous glucose monitoring system (CGMS) (Medtronic, CA). The aim of this study was to evaluate the accuracy of CGMS in children and adolescents with type 1 diabetes mellitus (DM1) and the efficacy of this method to detect unrecognized hypoglycemia in this population. It were analyzed capillary glycemia (CG) and CGMS sensor's value; glycemic excursions; postprandial hyperglycemia; unrecognized hypoglycemia; complications and therapeutic management after CGMS. A1c levels were measured at the start and after 3 months of the study. Correlation coefficient during hypo, hyper, and normoglycemia and sensitivity/specificity was determined. The mean CG values were 213.8 ± 63.4 mg/dl vs. 209.7 ± 52.5 mg/dl by sensor, with statistical significance by Pearson's correlation ($p < 0.001$). There was no difference between CGMS and CG value in order to detect glycemic excursions ($p = 0.32$). The postprandial hyperglycemia and unrecognized hypoglycemia was detected in 66.7% and 56.2% of this patients, respectively. The correlation coefficient during hypoglycemia presented no statistical significance by Pearson's correlation ($p = 0.29$) vs. during hyperglycemia ($p = 0.001$). The CGMS sensor presented low sensitivity (63.3%) to detect hypoglycemia. This data showed important decreased level of A1c in this population 3 months after CGMS with statistical significance ($p = 0.03$). The CGMS showed to be a very safe method, well tolerated, with high accuracy in glycemic values and low complications rate. This results suggest that CGMS is a good method to identify postprandial hyperglycemia, to improve metabolic changes in therapeutics with significant impact in A1c of diabetic pediatric patients. This data confirmed the low sensitivity of CGMS to detect unrecognized hypoglycemia in pediatric DM1 patients. (Arq Bras Endocrinol Metab 2005;49/4:569-574)

Keywords: Continuous glucose monitoring system; Unrecognized hypoglycemia; Children/adolescents; Diabetes mellitus type 1

RESUMO

Eficácia da Monitorização Subcutânea Contínua da Glicemia (CGMS) na Detecção da Hipoglicemia Assintomática em Crianças e Adolescentes com Diabetes Tipo 1.

Foram estudados retrospectivamente 17 pacientes ($15,76 \pm 4,5$ anos) submetidos a monitorização subcutânea contínua da glicemia (CGMS) (Medtronic; CA) por 72 horas. Buscou-se avaliar a acurácia da CGMS em crianças e adolescentes com diabetes mellitus tipo 1 (DM1) e sua eficácia na detecção de hipoglicemia assintomática nesse grupo de pacientes. Foram analisados os valores de glicemia capilar (GC) e pelo sensor CGMS; excursões glicêmicas; hiperglicemia pós-prandial; hipoglicemia assintomática; complicações e conduta após a CGMS. Os níveis de A1c foram determinados antes e 3 meses após a CGMS. A correlação sensor/glicemia capilar foi avaliada durante normo, hipo e hiperglicemia, bem como a sensibilidade e especificidade. A GC média durante a CGMS foi de $213,8 \pm 63,4$ mg/dl vs. $209,7 \pm 52,5$ mg/dl detecta-

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da pelo sensor, com correlação de Pearson significativa ($p < 0,001$). Não houve diferença significativa entre a CGMS e GC na detecção de excursões glicêmicas ($p = 0,32$). A hiperglicemia pós-prandial e hipoglicemia assintomática foram identificadas em 66,7% e 56,2% dos pacientes durante a CGMS, respectivamente. A correlação entre sensor CGMS e GC durante hipoglicemia assintomática mostrou-se não significativa ($p = 0,32$) vs. durante hiperglicemia ($p = 0,001$). O sensor CGMS apresentou baixa sensibilidade (63,3%) para detecção de hipoglicemia assintomática. Observou-se redução significativa da A1c três meses após a CGMS em crianças e adolescentes com DM1 ($p = 0,03$). A CGMS mostrou-se método seguro, bem tolerado, com alta acurácia nos valores glicêmicos detectados, com baixo índice de complicações. Esses dados comprovam a alta eficácia da CGMS na detecção de hiperglicemia pós-prandial, na redução da A1c e melhora do controle metabólico, com baixas sensibilidade para na identificação de hipoglicemia assintomática em crianças e adolescentes com DM1. (Arq Bras Endocrinol Metab 2005;49/4:569-574)

Descritores: Monitorização subcutânea contínua da glicemia; Hipoglicemia assintomática; Crianças / adolescentes; Diabetes mellitus tipo 1

THE MAJOR INCONVENIENCE of self-monitoring of blood glucose (SMBG) in clinical practice is due to the fact that blood glucose is only intermittently measured by fingerstick capillary glycemia from which only a partial and therefore incomplete picture of blood glucose fluctuations can be made (1,2). Because of many factors, including pain and inconvenience, many children with diabetes do not accept frequent fingersticks for SMBG (3). The availability of the Continuous Glucose Monitoring System (CGMS) (Medtronic; Northridge, CA) offers the opportunity for pediatric type 1 diabetic patients to match the demands of intensive therapy with the intensive monitoring of blood glucose levels (1,2).

The DCCT (Diabetes Control and Complications Trial) established that intensive and multidisciplinary treatment of type 1 diabetes mellitus (DM1) improved metabolic control and reduces the complications of disease (4). Estimates showed that a significant damage in quality of life is frequently due to DM1 in children and adolescents, include function limitations, social stress, even mayor depression (2). Psychological aspects and children's acceptance of DM1 may exercise some influence in their glycemic control (5).

Despite an excellent A1c levels and target preprandial glucose levels, pediatric diabetic patients often experience unrecognized hypoglycemia and

postprandial hyperglycemia that are not evident with routine monitoring (6). In addition, families frequently do not measure blood glucose levels during the night and 55% of severe hypoglycemic events in the DCCT occurred during sleep (7). Several studies demonstrated the utility of the CGMS to improve metabolic control, to detect more glycemic excursions (hypo and hyperglycemia) and to detect more postprandial hyperglycemia than SMBG (8-12). The efficacy of CGMS in detecting hypoglycemia is not well established in medical literature (13-15).

There were no information in Brazil about the effects of CGMS in pediatric type 1 diabetic patients. This study aimed to determine the accuracy of CGMS and the efficacy of this method to detect unrecognized hypoglycemia in DM1 pediatric patients. The complications of CGMS in children and adolescents are still discussed.

SUBJECTS AND METHODS

Patients

This retrospective study assessed 17 diabetic patients (15.76 ± 4.52 years), duration of DM1: 2.0-18.0 years, mean duration of 7.42 ± 4.93 years, submitted to 72 hours CGMS (Medtronic; Northridge, CA). Each child had a mean A1c level $> 7.0\%$ (range: 7.0%-10.9%) for the 3 months before participating in the study. All participants were on intensive insulin treatment with 29.4% receiving continuous subcutaneous insulin infusion (insulin pump therapy) and 70.6% receiving multiple daily injections (MDIs). There were 64.7% ($n = 11$) of females and 35.3% ($n = 6$) of males.

Glucose Sensor

The MiniMed Meditronic (Northridge, CA) CGMS, the first model approved by FDA (Food And Drug Administration, EUA) was used for subcutaneous glucose monitoring. The glucose is measured by an electrochemical assay of glucose-oxidize detecting values range from 40 to 400mg/dl. The system consists of a subcutaneous sensor connected by a cable to a pager-sized glucose monitor. Glucose readings are acquired by the monitor every 10 seconds and an average glucose value is stored in the monitor memory once every 5 minutes (up to 288 measurements per day and 864 in all exam). Each glucose sensor provides glucose information for up to 72 hours. After the initial 60 minutes, the electrical current in nanoamper is converted in glucose value after the information of this measured in the monitor. The stored values in the

monitor are downloaded by the MiniMed Com-Station and presented in graphical and statistical form via a computer program and the sensor is eliminated. The original Medtronic MiniMed glucose sensor was modified in November 2002. This modification resulted in improved accuracy. In this study was utilized the new modified sensors.

Procedure

All patients were submitted to basic orientations of CGMS function and the register of all events in a "patient diary", by one person (F.F.R.M). During the CGMS, all participants had to perform at least four capillary glycemic tests per day and enter these values into the CGMS monitor to obtain correlation coefficients between the SMBG and the CGMS values. All SMBG tests were performed using the digital glucometer (Accu-Chek Active; Roche Diagnosis). The first capillary glycemia entered in the monitor were realized after 60 minutes of CGMS. Families were asked to not change their dietary practices during the study.

It were analyzed: correlation coefficient (%); mean absolute difference (MAD); number of sensor's readings; duration of exam (h); mean capillary glycemia (CG) and mean CGMS sensor's glycemic value; glycemic excursions; postprandial hyperglycemia (NR< 140mg/dl); unrecognized hypoglycemia; A1c levels at start and after 3 months; complications (trauma, local infection, disconnection); dropped the method; therapeutic management after CGMS.

The correlation coefficient and MAD were calculated by Medtronic software analysis and defined by > 0.79% and < 28%, respectively, to meet the optimal accuracy criteria. The MAD was determined by the average value of differences between sensor's glucose values and blood glucose values in percentage (%) for a given day. The number of measurements by CGMS was considered significant higher than 80% (> 640 readings/72h).

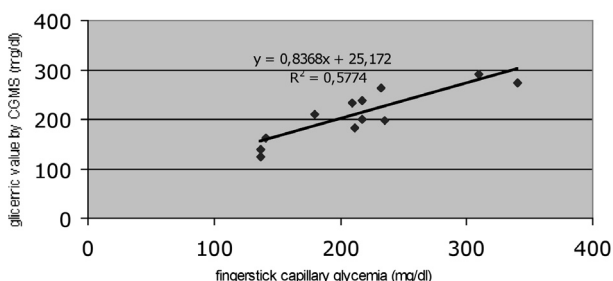


Figure 1. Correlation of glycemic values detecting by continuous glucose monitoring system (CGMS) sensor vs. fingerstick values in type 1 pediatric diabetic patients ($r^2=0,57$; $P<0,001$).

The glycemic excursions were based on patients information and correlated by CGMS register. Hypo and hyperglycemia were defined as blood glucose < 70mg/dl and > 180mg/dl, respectively. The duration of hypo, hyper and normoglycemia were registered in hours/percent for comparison effect. The postprandial hyperglycemia was considered when blood glucose values were over than 140mg/dl two hours after lunch. The unrecognized hypoglycemia was detected by glycemia < 70mg/dl without clinical symptoms. The accuracy of CGMS sensor was based on comparison of capillary glycemic values and sensor's values by the Pearson's correlation during hypo, normo and hyperglycemia, with P value < 0.05. The sensitivity and specificity of sensor's value for hypo, hyper and normoglycemia was determined by statistical analysis.

The A1c values were determined at the start and at the 3-month after the CGMS in 13 patients. A1c values were determined using the HPLC instrument, with a normal range of 4.3% to 6.9%.

The complications during the CGMS were based in medical observation and patients information. It were analyzed the complications during the sensor implantation (bleeding and pain) and during the exam (trauma, local infection, disconnection, psychological aversion, technical deficiency, others "alarms"), dropped of the method and therapeutic management after CGMS.

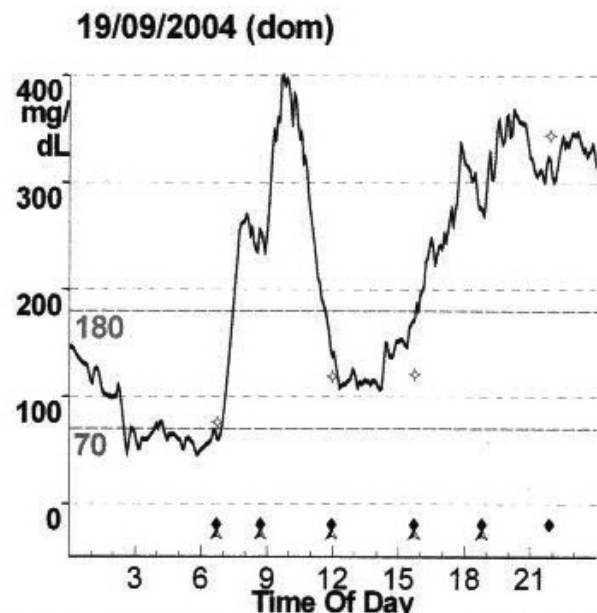


Figure 2. CAG, female, 10 years old, submitted to CGMS (19/09/2004) with detection of asymptomatic nocturnal hypoglycemia (prolonged) and postprandial hyperglycemia.

Statistics

The data was collected and analyzed by Minitab software, by *t* test, Qui-square test, Pearson's correlation and regression test. It was considered significant an *p* value < 0.05.

RESULTS

The number of glucose readings during CGMS was 799.8 ± 189.9 (VR > 680), with significant value in 88.3% of patients. The mean number of hours per sensor was 71.8 ± 9.7 hours. The correlation coefficient between SBGM and CGMS values was 0.93 ± 0.04 (normal range, NR > 0.79), with ideal values in most of 94.12% of patients studied. About the MAD, the mean value was $13.6 \pm 3.5\%$ (NR < 28%), significant in 88.3% of patients. The main reason for the higher numbers of usable CGMS data were patient compliance, with successful to enter the ideal minimum four SMBG levels each day.

The mean capillary glucose values were 213.8 ± 63.4 mg/dl vs. 209.7 ± 52.5 mg/dl by CGMS sensor, with statistical significance detected by Pearson's correlation (*p* < 0.001) (figure 1).

About the glycemic excursions, the CGMS was not more efficient in detecting glycemic excursion than fingerstick capillary glycemia (*p* = 0.32). The postprandial hyperglycemia was identified in 66.7% of pediatric type 1 diabetic patients with mean value of 187.0 ± 77.4 mg/dl (NR < 140mg/dl). The unrecognized hypoglycemia was detected in 56.3% of this patients (figure 2). During the 72h CGMS, the patients were in state of hyperglycemia during 57.3 ± 29.4% of the register (table 1).

The correlation of blood glucose values and CGMS sensor's value during hypoglycemia showed low rate of concordance and presented no statistical

significance by Pearson's correlation (*p* = 0.29) vs. during hyperglycemia (*p* < 0.001) or normoglycemia (*p* = 0.004). The CGMS sensor presented low sensitivity (63.3%) and high specificity (96.9%) to detect hypoglycemia (table 2).

The evaluation of A1c levels in 13 (76.5%) patients before the CGMS and after 3 months showed significant decreased level of A1c in this population (8.30 ± 1.1 vs. 7.32 ± 0.9 ; *p* = 0.03).

No complications were registered in 94.1% of patients. The disconnection sign was the most common in this case (11.8%). No trauma, local infection, allergy, bleeding or other were registered during CGMS in this study. The psychological aversion and technical deficiency were not observed in this population. All patients (100%) completed the CGMS integrally.

The therapeutic management of pediatric type 1 diabetic patients was changed in 100% of patients, including insulin adjust dose, change of insulin type, institute nutritional and psychology support and physical activity approach.

DISCUSSION

This study is the first report of accuracy, utility and complications of CGMS in pediatric patients in Brazil. In the present study, all patients who used the CGMS showed some decline in A1c after 3 months, in agreement to Ludvigsson et al. (15). After 3 months, the decrease in mean A1c levels for the CGMS group was from 8.18% to 7.28%, similar to Ludvigsson et al. findings (15). In this data, we observed a total adherence to CGMS, with no interruption during the procedure.

This data showed high accuracy of CGMS vs. capillary glycemia, similar to medical literature (8-12). Sachedina & Pickup (2003) demonstrated the correlation of sensor's and fingerstick's values in 18 DM1

Table 1. Duration of hyper, hypo and normoglycemic state during continuous glucose monitoring system (CGMS) in 17 children and adolescents with type 1 diabetes.

		Duration of Glycemic State during CGMS 72h	
		Minutes	%
Hypoglycemia	(< 70mg/dl)	224 min.	4.7 ± 3.39
Normoglycemia	(70-180mg/dl)	1650 min.	38.0 ± 27.9
Hyperglycemia	(> 180mg/dl)	2446 min.	57.3 ± 29.4

Table 2. Sensitivity and specificity of continuous glucose monitoring system (CGMS) to detect hypo, hyper and normoglycemic state in 17 type 1 diabetic pediatric patients.

Glycemic State		Sensitivity (%)	Specificity (%)	<i>p</i> value
Hypoglycemia	(< 70mg/dl)	63.3	96.6	0.29
Normoglycemia	(70-180mg/dl)	89.4	89.7	0.004
Hyperglycemia	(> 180mg/dl)	91.4	95.4	< 0.001

patients submitted to 72h CGMS. The CGMS showed to be better than intensive CG (8 times per day) in detection of asymptomatic hypoglycemia and postprandial hyperglycemia, in agreement with our data (16). We verify a correlation coefficient of 0.93, with significant value in more than 90% of patients, corroborated by Djakoure-Platonoff et al. (2003) (17). They obtained correlation coefficient of 0.92, with significant value in 93% of cases and MAD of 25%. This group considered the 72h CGMS method of high accuracy and gold standard in determination of glycemic profile in diabetic persons.

Guerci et al. reported the accuracy, performance, and reproducibility of the CGMS in 18 type 1 diabetic patients submitted to 72-h CGMS, with mean duration of CGMS recording of 63 ± 12 h, 692 pairs of data for glucose meter readings and CGMS, correlation coefficient ranging from 0.87 to 0.92 (NR > 0.79) (18).

In pediatric patients, the CGMS showed to be a very safe method and an important alternative to promote decrease of A1c levels, therapeutic adjustment, education and motivation of patients (17). In EUA, 12 diabetic adolescents (A1c > 8%) were studied and submitted to 72h CGMS. The CGMS promoted detection of glycemic excursions in all patients, postprandial hyperglycemia in 10/12 cases and nocturnal hypoglycemia in 30% of patients. After two months, they observed a significant decrease of A1c levels (6,20). This data were very similar to our findings in Brazilian pediatric type 1 diabetic patients.

About the CGMS sensor efficacy in detecting glycemic excursions, this results corroborated to many studies in medical literature (21-24). This data showed that CGMS is very useful to detect postprandial hyperglycemia. Recent data of 91 DM1 patients estimated that the accuracy of CGMS sensor is more effective in elevated glycemic levels than hypoglycemic state (21).

The efficacy of CGMS in detecting hypoglycemia is not well established in medical literature (13-15). Boland et al. (2001) detected unrecognized hypoglycemia in 70% of 56 type 1 diabetic children submitted to 72h CGMS and considered this method a gold standard in hypoglycemia management in pediatric population underwent only to SMBG (23). Guerci et al. observed a low sensitivity of CGMS sensor to detect hypoglycemic levels (33%) in diabetic patients (18).

According to McGowan et al. (2002), the CGMS sensor presented low efficacy in detecting hypoglycemia in adolescents with DM1. The correlation coefficient during hypoglycemic episodes showed only 0.76 (NR > 0.79) of concordance and has to be analyzed with attention (14). Kovatchev et al. (2004)

revealed that the accuracy of sensor readings were lower in hypoglycemia (73,5%) versus euglycemia (99%) and hyperglycemia (95.4%), with failure to detect hypoglycemia like the most common error during the test (13). In this data, the correlation between capillary glucose and sensor's glucose values during hypoglycemia showed no significance ($p= 0.29$) vs. during hyperglycemia ($p< 0.001$), with low sensitivity (63.3%) of CGMS sensor for hypoglycemic state, corroborating value to McGowan, Guerci and Kovatchev groups (13,14,18).

Chico et al. (2003) reported the useful of CGMS in detecting unrecognized hypoglycemia and improving metabolic control in 70 diabetic patients submitted to 72h CGMS. The CGMS detected unrecognized hypoglycemia in 62.5% of the type 1 diabetic patients and in 46.6% of the type 2 diabetic patients and in both were observed significant decrease levels of A1c after 3 months, similar to our data. This findings suggest that CGMS is useful for detecting unrecognized hypoglycemia in diabetic patients and improve metabolic control (24).

In a recent study of nocturnal hypoglycemia in 50 children with diabetes who were hospitalized overnight, it was found that 47% had a blood glucose level below 60mg/dL (< 3.3mmol/L) during the night (using hourly blood glucose determinations) (25). They found that 49% of cases were asymptomatic. The data from Ludvigsson et al. suggest that the incidence of asymptomatic episodes is closer to 85% (17 of 20) (15).

No complications were registered in almost 95 percent of patients. No trauma, local infection or bleeding were registered. The insulin therapeutic regimen was adjusted in 100% of patients. In Guerci et al. analysis, the disconnection was the most common problem detected during CGMS, without any side effects reported at the site of sensor implantation (18). In this study, the disconnection was the most common problem detected during CGMS in this data, agreed with Guerci et al. Ludvigsson et al. observed some failed to enter the minimum 4 SBGM values during the day and that usable data were not obtained (15). In this data, all the children completed at least 4 fingerstick values entered to the monitor, promoting high accuracy of CGMS values.

CONCLUSIONS

This study suggest that CGMS is a very good method to identify postprandial hyperglycemia and to improve metabolic changes in therapeutics with significant

impact in A1c levels of pediatric type 1 diabetic patients. The CGMS is a very safe method, well tolerated by patients, with low accuracy in detecting hypoglycemic state. This data confirmed the low efficacy of CGMS in detecting unrecognized hypoglycemia in pediatric type 1 diabetic patients.

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