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Real time continuous glucose monitoring in critically ill patients - a prospective, randomized trial

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Short running title: Online glucose monitoring in the critically ill

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Objective **-** To evaluate the impact of real time continuous glucose monitoring (CGM) on glycemic control and risk of hypoglycemia in critically ill patients.

Research Design and Methods **-** 124 mechanically ventilated patients were randomly assigned to the real time CGM group (n=63; glucose values given every five minutes) or to the control group (n=61; selective arterial glucose measurements according to an algorithm; simultaneously blinded CGM) for 72 hours. Insulin infusion rates were guided according the same algorithm in both groups. Primary endpoint was percent of time below a glucose level of 110 mg/dl. Secondary endpoints were mean glucose levels and rate of severe hypoglycemia (< 40 mg/dl).

Results **-** Percent of time below a glucose level of 110 mg/dl (59.0 ± 20% vs. 55.0 ± 18% in the control group; p=0.245) and the mean glucose level (106 ± 18 mg/dl vs. 111 ± 10 mg/dl in the control group, p=0.076) could not be improved using real time CGM. Rate of severe hypoglycemia was lower in the real time CGM group (1.6% vs. 11.5% in the control group, p=0.031). CGM reduced the absolute risk of severe hypoglycaemia by 9.9% (95% CI 1.2–18.6) with a number needed to treat of 10.1 (95% CI 5.4–83.3)

Conclusions - In critically ill patients, real time CGM reduces hypoglycemic events but does not improve glycemic control compared to intensive insulin therapy guided by an algorithm.

Hyperglycemia, a frequent finding in up to 90% of all critically ill patients, is associated with increased morbidity and mortality (1,2). In three monocentric studies, intensive insulin therapy to achieve and maintain normoglycemia resulted in decreased morbidity and mortality (3-5). However, two subsequent multicenter studies failed to adequately reach normoglycemia and were prematurely stopped because of safety reasons with increased rates of severe hypoglycemia (6,7). Whereas in a recent trial intensive insulin therapy resulted in improved short term outcome in paediatric intensive care, another recent trial demonstrated increased mortality among adults under intensive glucose control (5,8). An updated meta-analysis of 26 randomized trials including 13567 patients reported that intensive insulin therapy had no effect on the overall risk of death but simultaneously resulted in a 6-fold increased risk of severe hypoglycemia. Currently, there is still an intense and conflicting discussion on the difficulty to obtain near normoglycemia thereby avoiding the risk of severe hypoglycemia (9). –In critically ill patients an accurate real time CGM might be the best way to minimize a consistently reported increased rate of severe hypoglycemia associated with intensive insulin therapy and to increase effectiveness and safety of tight glucose control.

Numerous studies in diabetic patients tested continuous glucose monitoring (CGM) devices and demonstrated high accuracy of the CGM derived glucose values compared to blood glucose measurements (10-12). In particular, these devices were highly sensitive to detect rapid glucose excursions (12). Recently, these CGM techniques have been also evaluated in critically ill patients and yielded similar positive results (13-17). Mainly, subcutaneous CGM devices have been intensely investigated (13-17). Accuracy and reliability of a subcutaneous CGM device could be demonstrated both in critically ill patients with and without circulatory shock (16). Subcutaneous CGM worked equally both in patients without and with norepinephrine therapy. Validity of the subcutaneous CGM under norepinephrine therapy was furthermore independent of levels of blood glucose values, severity of illness and patients' Body Mass Index (BMI) (16). Using this subcutaneous CGM device approximately 99% of all measured sensor glucose values were within the acceptable treatment zone according to an insulin titration grid analysis (16).

Based on these underlying data, we hypothesized that subcutaneous real time CGM improves glucose control simultaneously reducing the risk of hypoglycemia.

RESEARCH DESIGN AND METHODS

Patients and Setting - The study was performed in the Intensive Care Unit (ICU) of the Department of Medicine III at the Medical University Hospital of Vienna. Patients were recruited between June 2006 and August 2008.

Patients were eligible for inclusion in the study within 24 hours after ICU admission if they were older than 18 years of age, intubated, mechanically ventilated and expected to stay more than 48 hours on the ICU after initiation of intensive insulin therapy. Patients were not enrolled in the study if any of the following criteria were present: expected ICU stay less than 48 hours, not expected to be mechanically ventilated more than 48 hours, arterial glucose values within the normal range (80 to 110 mg/dl) before enrolment, enrolment in another study and no availability of a CGM device during the screening phase. The study protocol was approved by the research ethic committee of the Medical University of Vienna. According

to the Austrian law and the guidelines of the research ethic committee written informed consent was obtained from patients after regaining consciousness.

Research design - Intensive insulin therapy to maintain normoglycemia (80 to 110 mg/dl) was performed by the nurses in all included patients. In the control group intensive insulin therapy was performed strictly according to a previously described insulin titration algorithm (18). In short this algorithm is a slightly modified version of the algorithm used in the Leuven-studies (3,4). It prescribes both insulin infusion rate, time of next glucose measurement and in case of hypoglycemia, dextrose administration depending on glucose levels and glucose trends. Consequently, it defines nine different states requiring different actions, though leaving space for interpretation (for the responsible nurse) since it includes dynamic variables like glucose trends. In the control group selective arterial blood glucose measurements were done according to the algorithm (18). On the basis of these arterial blood glucose values nurses guided intensive insulin therapy. A continuous intravenous insulin regimen was used in all patients (Insulin Aspart, Novo Nordisk®). Nutritional support was standardized in all patients according to a nutritional protocol. Energy requirements were calculated with 25 kcal per kg bodyweight per day. For every patient included following data were documented: age, sex, ICU admission reasons, height, weight, BMI, cumulative fluid balance and insulin use during study period, norephinephrine therapy, co-medication including dextrose infusion, length of ICU stay, ICU and hospital mortality. Severity of illness was assessed by the SAPS II Score and the SOFA Score (19,20).

Continuous glucose monitoring - Within 24 hours after ICU admission eligible patients were randomly assigned, in a 1:1 ratio, to the real time CGM group or to the control group. Responsible ICU staff was informed about inclusion of patients. Additionally a user manual of the CGM was placed at the bed-side. In the real time CGM group glucose values were given every five minutes by the subcutaneous real time CGM system for 72 hours (Guardian®, Medtronic, Northridge, CA). On the basis of these displayed subcutaneous glucose values nurses guided insulin therapy according to the recommended insulin dose of the insulin titration algorithm in the real time CGM group, too (18). However, in the intervention group nurses were requested to take real time glucose readings in close intervals according to clinical necessity at personal discretion however at least every two hours in contrast to the control group. In the control group simultaneously blinded subcutaneous continuous glucose reading by the CGM System Gold™ (Medtronic, Northridge, CA) was performed for 72 hours. These subcutaneous glucose values were blinded to ICU staff and were retrospectively downloaded to a computer using the Minimed Com-Station® and a special program (Minimed Solutions™ Software CGMS® Sensor MMT-7310, Medtronic Minimed, Northridge, CA). Stored glucose data of the real time CGM system (Guardian®, Medtronic, Northridge, CA) were also downloaded (Guardian™ Solutions™ Software, MMT-7315 Version 2.16D, Medtronic Minimed, Northridge, CA) The CGM system used in both groups consists of the same technology and comprises a holter-style sensor system, a pager-size glucose monitor and a disposable subcutaneous needle-type enzymatic glucose electrode connected to the monitor. In all patients the sensor was placed subcutaneously in the lateral abdominal region using the Sen-Serter® device (Medtronic Minimed, Northridge, CA). The actual glucose level was displayed on the monitor screen only in the real time CGM group using the

Guardian®. No alarm levels were set. The first pair of arterial blood glucose/sensor glucose values, which was used for initial calibration of the CGM system was not used for statistical analysis. According to the manufacturer's instruction manual both CGM systems were calibrated against arterial blood glucose measurements four times per day (every five to six hours). Arterial blood glucose measurements were obtained using an automated blood gas analyzer (Radiometer ABL 700®, Copenhagen, Denmark). Subcutaneous sensors were planned to stay in place for 72 hours. The place of insertion was inspected daily for local irritations, bleeding and infection.

Statistical analysis - Sample size was calculated using the GraphPad StatMate software program (GraphPad Software, Inc., San Diego, USA). Anticipated proportions were compared with the chi-square-test. The anticipated proportion was 0.57 for the control group and 0.80 for the real time CGM group. Alpha was 0.05 (two-tailed). A sample size of 120 was calculated for a power of 80%. 10 drop outs were calculated. A drop out was defined as removal of the CGM sensor within 12 hours after insertion.

Data are presented as mean ± standard deviation or as absolute and relative frequency as adequate. Baseline data were compared qualitatively to assess successful randomisation and quantitatively by t-tests or Fisher's exact tests as appropriate. The primary endpoint was percent of time below the glucose level of 110 mg/dl. This variable was normally distributed therefore a t-test was used to test the null hypothesis of no difference. Secondary endpoints were mean glucose level, median time from start of intensive insulin therapy to achievement of normoglycemia, incidence of hypoglycemia (defined as glucose level below 40 mg/dl) and percent of time below a glucose level of 150 mg/dl. The effect of the intervention versus standard therapy was estimated as risk ratio with a 95% confidence interval. The Fisher's exact test was used to test the null hypothesis of no effect.

For subgroup analyses stratum specific effects of the intervention versus control on the primary endpoint were calculated. To assess differences between subgroups p-values for interaction by using linear regression models including interaction terms of the group allocation subgroup variable were calculated.

For data management and analysis MS Excel for Windows and Stata (Stata Corp., College Station, Tx) 9.0 for Mac was used. A two-sided p-value less 0.05 was generally considered statistically significant.

RESULTS

Figure 1 shows the trial profile. Baseline demographics, patients` characteristics at ICU-admission and reason for ICU admission did not differ significantly between both groups (Table 1). Groups were well matched with respect to potentially blood glucose influencing co-medication (hydrocortisone: 25 vs. 30 patients, p=0.4754; propofol 34 vs. 41 patients, p=0.3588; norepinephrine 39 vs. 34 patients, p=0.278; enteral nutrition 57 vs. 59 patients, p=1.0; parenteral nutrition 4 vs. 4 patients, p=1.0; control group vs. real time CGM group, respectively). Drop-outs (sensor time < 12 hours) did not occur. In nine patients sensors were accidentally removed after 12 to 48 hours. Data of these nine patients were analysed until accidental removal of sensors. Table 2 shows blood glucose control in both treatment groups. The primary endpoint percent of time below 110 mg/dl and the secondary endpoints mean sensor and blood glucose levels, as well as percent of time below 150 mg/dl were not different in both groups. Baseline glucose values, time to reach the target glucose value of 110 mg/dl and insulin dose during the study period were also not different. Rate of hypoglycemia was significantly lower in the

real time CGM group than in the control group (1.6 vs. 11.5%; p=0.0312). Relative risk reduction for severe hypoglycemia is 86% (95%CI 21–98%) using the real time CGM. This denotes an absolute risk difference of 9.9% (95%CI 1.2–18.6) and a number needed to treat (NNT) of 10.1 (5.4–83.3). All patients with hypoglycemic events just experienced one episode of hypoglycemia except one patient in the control group, who experienced two episodes (on day 2 and 3 of the study period). Glucose measurements were performed 1228 times in the control group. Glucose readings of the real time CGM were taken 1772 times. According to the insulin therapy algorithm the glucose measurements in the control group and glucose readings in the real time CGM group were distributed (in the algorithm defined states) in the following way: glucose >140 mg/dl: 118 glucose measurements vs. 221 glucose readings; p=0.017; range 110-140 mg/dl: 32 glucose measurements vs. 98 glucose readings; p=0.0002; approaching target range #1: 117 glucose measurements vs. 155 glucose readings; p=0.5049; approaching target range #2: 226 glucose measurements vs. 367 glucose readings; p= 0.1274; steady in the target range: 585 glucose measurements vs. 780 glucose readings; p=0.0574; decreasing steeply: 22 glucose measurements vs. 57 glucose readings; p=0.0223; glucose range 60-80 mg/dl: 90 glucose measurements vs. 57 glucose readings; p<0.0001; glucose range 40-60 mg/dl: 32 glucose measurements vs. 36 glucose readings; p=0.3618; glucose <40mg/dl: 6 glucose measurements vs. 1 glucose reading; p=0.0428. Glucose measurements/readings are given as control group vs. real time CGM group, respectively.
Dextrose 33% was administered one time in the real time CGM group and 6 times in the control group. In 2 patients in the control group hypoglycemic events remained unrecognized and were only recorded by the blinded CGM. In these 2 patients blinded CGM recorded a short hypoglycemic event after an anti-hypoglycemic action of the nurse (stop of the i.v. insulin, assurance of glucose intake), whereas next blood glucose measurement (after one hour) already showed an increased blood glucose value.

Subgroup analysis revealed a significant benefit concerning the primary endpoint (percent of time below 110 mg/dl) from real time CGM for patients with a SOFA-score > 11 (64.4% vs. 54.7%; p=0.025) and for patients with a positive fluid balance > 6000ml during the study period (62.7% vs. 51.9%, p=0.031). Differences for all subgroups are given in the Online Appendix Figure A (available at http://care.diabetesjournals.org). Local complications at the sensor insertion site did not occur.

CONCLUSIONS

Management of hyperglycemia in critically ill patients is one of the most contradictorily discussed topics in intensive care medicine for the last years (9). Although it is generally accepted that stress hyperglycemia is associated with increased morbidity and mortality, it is still uncertain whether tight glycemic control is beneficial or even harmful for critically ill patients (1,2,6-8). Irrespective of the selected blood glucose target range, all randomized clinical studies failed to reach their predefined target range in the majority of patients and resulted in an increased rate of severe hypoglycemia (6-8). Thus, a real time CGM seems to be the optimal approach to increase effectiveness and safety of intensive insulin therapy in critically ill patients. However, in our prospective, randomized study glucose control could not be significantly improved using the real time CGM. Compared to previous studies glucose control in our control group was well performed possibly offering little space for improvement (13). This fact may be due to

the long term clinical experience with tight glycemic control on our ICU (16,18). Nevertheless, sample size calculation was based on the assumption that real time CGM would lead to a 23 percent improvement in glucose control. This goal was definitely failed. An obstacle for this may be imperfect adherence to the given order to check online glucose values at least every two hours. We attached great importance to this order, however, a nurse to patient ratio of 1:2 on our ICU and a pressure of work especially during the night shift may have weakened the order. Although more glucose readings in the real time CGM group led to a remarkable insulin infusion increase (more readings >140mg/dl and between 110 and 140 mg/dl) in the hyperglycemic range than in the control group, also more glucose readings required a remarkable reduction of the insulin infusion rate (more readings regarded as decreasing steeply) resulting in a lack of benefit concerning glucose control.

Another reason might be the omnipresent fear of hypoglycemic events. This fear seems to be justified because rate of hypoglycemia was 11.5% in the control group and blinded CGM was even able to reveal unrecognized hypoglycemic events, which were not detected by selective arterial blood glucose measurements according to the insulin titration algorithm.

Real time CGM however, was able to reduce severe hypoglycemic events significantly. In the real time CGM group more glucose readings were regarded as decreasing steeply according to the algorithm. According to our algorithm this requires a remarkable reduction (by half) of the insulin infusion rate and an early (one hour) next glucose measurement/reading. In the control group however, more glucose values occurred between 60 and 80 mg/dl. According to the algorithm glucose values between 60 and 80 mg/dl only required a reduction of the insulin infusion rate by 0.5IU/h (no 1 hour glucose measurement order). These two facts might have contributed to the prevention of hypoglycemic events in the real time CGM group and led to hypoglycemic events in the control group. Glucose trends are recognized easily with the real time CGM system since glucose values (mean of every 5 minutes) of the last two hours can be viewed on the monitor. Reduction of severe hypoglycemic events was significant with a NNT of 10 using the real time CGM. Real time CGM is therefore a suitable instrument to improve patients' safety while practicing intensive insulin therapy. This point is of major importance since high rates of (recognized) severe hypoglycemia have been criticized in all studies concerning tight glycemic control (3-8). The most recent multicentric clinical trial indicated even harmful effects of tight glycemic control possibly mediated by an increased rate of hypoglycemia (8). The results of our study now suggest that negative effects of intensive insulin therapy might also be conveyed by up to now unrecognized hypoglycemic events. Real time CGM offers the possibility to perform clinical trials using intensive insulin therapy without increased rates of severe hypoglycemia because it is not only able to detect but to prevent them.

Real time CGM was not able to shorten time to reach blood glucose values below 110 mg/dl in our study. However, time to reach target blood glucose levels in our study, which was 118 and 150 min respectively, is regarded as adequate time to reach the target from our point of view. An even more rapid achievement of the target range increases the risk of overshooting resulting in both more hypoglycemic and consequently more hyperglycemic events. Since high glucose variability has also shown to be associated with higher mortality in critically ill patients, overshooting insulin therapies and too rapid glucose changes might be avoided (21).

Subgroup analysis showed a significant beneficial effect on the primary endpoint in the most severely ill patients. Additionally, although not statistically significant, patients in the real time CGM group with a SAPS II Score greater than 59 had a higher percent of time with a glucose level below 110 mg/dl. In one of our previous studies we could demonstrate, that tight glycemic control was less successfully reached in more severely ill patients (16). In this special group of ICU patients blood glucose levels may be more fluctuant and delicate. Therefore, we assume that especially the sickest ICU patients may benefit from the real time CGM.

Validation studies of the subcutaneous CGM have shown accuracy and reliability not only in patients with diabetes but also in patients with cystic fibrosis and critically ill patients (10-13,16,17,22,23). Several outcome studies using real time CGM in type 1 diabetes and pregnant women with diabetes indicated promising results concerning improved glucose control but also increasing patients' safety by reducing hypoglycemic events (24,25). Therefore, more research into continuous glucose monitoring to improve ease of use and safety of intensive insulin therapy also for critically ill patients is highly demanded.

A limitation of the study is the relatively small number of patients included. The number was adequately calculated for our primary endpoint, however much more patients are required to assess possible benefits of CGM on morbidity and mortality. Another aspect might be the short duration of our intervention, which was limited to one sensor lifetime of 72 hours.

Monocentric design of the study may also be a limitation due to long term experience of all groups of health professionals on our ICU, performing intensive insulin therapy since years in a very cooperative and successful way (18). Other settings less experienced and less successful in intensive insulin therapy might therefore benefit even more from the application of real time CGM.

A further limitation might be the use of the same insulin titration algorithm with respect to the insulin infusion rate in both the control group and the real time CGM group. Future studies might benefit from the development of a new algorithm including guidelines for insulin adjustment and readjustment, guidelines for next time to use CGM data and guidelines for offsetting trends versus reacting to measured results when using real time CGM.

The results of our study indicate that real time CGM increases safety of tight glycemic control in critically ill patients by significantly reducing severe hypoglycemic events. However, real time CGM could not improve glucose control defined as percent of time below 110 mg/dl.

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This prospective, randomized study was investigator-initiated and investigator-driven. Commercial entities had no role in study design, patient enrolment, data collection, data analysis, data interpretation, or writing of the report.

Disclosure: All authors declare that they have no conflict of interest.

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Figure legend:
Figure 1: Trial profile : ICU=intensive care unit. CGM=continuous glucose monitoring. IIT=intensive insulin therapy. MRI=magnetic resonance imaging.

Table 1: Baseline characteristics

Variable	**Real time CGM (n=63)**	**Control (n=61)**	**p-value**
Admission reason –no.(% of patients in the category)			
Respiratory failure	15 (24)	13 (21)	-
CPR	12 (19)	15 (25)	-
Sepsis/Septic shock	13 (20)	12 (20)	-
Heart failure	8 (13)	11 (18)	-
Neurologic disease/ Coma	9 (14)	4 (7)	-
Pulmonary embolism	3 (5)	3 (5)	-
GI-bleeding/ALF	3 (5)	2 (4)	-
History of diabetes –no.(%)	12 (19)	12 (20)	1
Age (years)	58 ± 15	62 ± 16	0.168
Gender (female/male)	(20/43)	(26/35)	0.265
BMI (kg/m²)	27.1 ± 5.1	26.6 ± 3.8	0.501
SAPS II	59 ± 16	58 ± 17	0.891
SOFA	11.4 ± 3.8	10.82 ± 3.9	0.400
Baseline glucose value (mg/dl)	138.0 ± 21.4	140.8 ± 23.1	0.465
Baseline blood pH	7.39 ± 0.08	7.37 ± 0.11	0.280
Baseline lactate	1.32 ± 0.49	1.49 ± 1.07	0.260
Fluid balance (ml, study period) Median (IQR)	6475 (2585 - 8943)	5356 (1183 - 9440)	0.567
Baseline systolic blood pressure (mm/Hg)	124 ± 24	123 ± 22	0.881
Baseline diastolic blood pressure (mm/Hg)	62 ± 12	60 ± 11	0.272
Baseline norepinephrine dose (µg/kg/min)	0.12 ± 0.08	0.15 ± 0.16	0.956

Data are number (%) or mean ± SD, or median (IQR), unless otherwise stated. CGM=continuous glucose monitoring. CPR=cardiopulmonal resuscitation. GI=gastrointestinal. ALF=acute liver failure. BMI=Body Mass Index. SAPS= Simplified Acute Physiology Score. SOFA= Sepsis-related Organ Failure Assessment.

Table 2: Primary and secondary endpoints

	Real time CGM (n=63)	**Control (n=61)**	**p-value**
Mean sensor glucose (mg/dl)	105.8 ± 18.1	110.6 ± 10.4	0.076
Mean blood glucose (mg/dl)	113.2 ± 14.3	114.0 ± 11.0	0.731
Time of glucose <110 mg/dl (%)	59.0 ± 20.4	55.0 ± 18.0	0.245
Time of glucose <150 mg/dl (%)	94.2 ± 7.9	92.9 ± 8.4	0.395
Time to reach 110 mg/dl (min) Median (IQR)	150 (48-275)	118 (45-240)	0.557
Rate of hypoglycemia (% of patients)	1.6	11.5	0.031
Insulin (IU/ 72h - study period)	104 ± 78	110 ± 52	0.320
LOS	17.4 ± 14.4	16.8 ± 12.2	0.785
ICU-Mortality (%)	22	26	0.677
Hospital- Mortality (%)	33	31	0.849

Data are number (%) or mean ± SD, unless otherwise stated. CGM=continuous glucose monitoring. LOS=length of stay. ICU=intensive care unit.