Glucose sensing module - is it time to integrate it into real-time perioperative monitoring? An observational pilot study with subcutaneous sensors

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Aims. To explore the feasibility of subcutaneous continuous glucose monitoring (CGM) in perioperative settings and to evaluate the perioperative development of glycaemia in persons with diabetes mellitus or impaired glucose tolerance by means of CGM.

Methods. Monitoring by means of Guardian® REAL-Time CGMS (Medtronic, Northridge, USA) in 20 perioperative periods. Sensor was inserted on the day before surgery and continued for 3 days with some exceptions.

Results. Full implementation of the method was successful in the intensive care unit setting only. No electromagnetic interference and no side effects were found. The Wilcoxon signed-rank test revealed no significant difference between sensor and laboratory analyser values. Pearson's correlation coefficients of the values obtained by sensor and the Wellion Linus glucometer were 0.875 for the whole perioperative period, 0.866 for the intraoperative period and 0.903 for the first perioperative day. A decline in sensor accuracy on the 6th day was registered in one case. 16 monitored cases (80%) did not meet the criteria for safe plasma glucose range. Hypoglycaemia was found in 4 (20%) cases. There was an association between grade of the perioperative dysglycaemia and need for reoperation within the next 3 months. The most frequent perioperative glycaemic patterns are demonstrated.

Conclusion. Subcutaneous CGM is safe offering detailed insight into glucose homeostasis in the dynamic perioperative period. Laboratory confirmation of sensor plasma glucose concentration by approved laboratory analyser is still necessary. The potential benefits of maintaining patients within a safe glucose range should be confirmed by future studies.

Key words: perioperative glycaemic control, continuous glucose monitoring, stress-induced dysglycaemia, subcutaneous glucose sensors, diabetes mellitus, surgery

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INTRODUCTION

Plasma glucose (PG) homeostasis in intensive care settings is a subject of ongoing intense investigation.

In patients with diabetes mellitus (DM) or impaired glucose tolerance, stress-induced dysglycaemia is enhanced due to impaired glycaemia control mechanisms. Together with preexisting vasculopathy and immune response dysfunction, it is responsible for the more frequent postoperative complications in these patients.

The prevalence of both type 1 and type 2 DM is epidemically growing and persons with DM undergo surgical procedures more frequently than the normal population, with prolonged length of hospital stay and higher mortality rates. Improvement of their postoperative outcome is therefore a challenge for anaesthesiologists.

Hyperglycaemia (providing there is no external glucose input) is a metabolic marker of surgical stress and therefore the glycaemia trend should be of interest for all care providing medical staff.

The impact of degree of glycaemic control on clinical outcome has been studied intensively over the past decade and has been the subject of well-known controversies. Tight glycaemic control, adopted as a standard of care after the publication of the Leuven study¹ in 2001, was abandoned, after new randomized controlled trials revealed the high risk of severe hypoglycaemia^{2,3}. On the other hand, there is indisputable evidence linking uncontrolled perioperative hyperglycaemia with a negative outcome. It was also demonstrated that hyperglycaemia-decreasing interventions reduce morbidity and mortality in all patients, regardless of a prior history of diabetes⁴⁻⁹. Hyperglycaemia leads to fluid shifts, electrolyte dysbalances, ketoacidosis, hyperosmolarity, dehydration and impaired neutrophil function predisposing to infection and impaired wound healing. An additional benefit could result from more intensive insulin therapy – insulin is not only a glycaemia-reducing agent with anticatabolic effects but also a growing factor with substantial wound healing properties, observed even in topical application^{10,11}.

Current guidelines recommend a sensible (“reasonable, achievable, and safe”) glycaemia management with more liberal PG target values in the near-normal range between 4.4 - 10 and 11.1 mmol/L (79 - 180 or 200 mg/dL) (ref.¹²⁻¹⁵). The accent is on maintaining glycaemia stability with respect to the physiological circadian PG rhythm existing even in critically ill patients¹⁶. The consensus statement on glycaemic control in critically ill patients is regularly upgraded¹⁷. It is recommendable to adhere to these guidelines to avoid “preventable complications”¹⁸.

So far, there has been limited evidence on the occurrence of perioperative hypoglycaemia episodes, which could be difficult to avoid by the means of standard intermittent PG sampling.

To meet appropriate PG target in the dynamic perioperative period, frequent and exact PG monitoring is essential and therefore a proper monitoring technology needed.

Central laboratory devices (CLD), most accurate for that purpose, do not provide real-time data. The gold standard for the intensive care setting, an automated blood gas analyser, is not always available. Point-of-care meters can be an unreliable estimate for plasma glucose¹⁹, especially with hypotension and hypoperfusion²⁰ and could lead to harmful clinical errors especially in the hypoglycaemic range²¹. Many of them lack FDA-required accuracy standards and cannot be regarded as an exact measuring device during the perioperative haemodynamic and haemoglobin shifts^{22,23}. All these common types of monitoring are intermittent, their efficacy depends on the frequency of blood sampling and some of the dangerous PG deviations could remain undetected.

Intravenous blood glucose monitors are under development, but they possess risks associated with intravenous or even central venous access, potential interference with i.v. solutions, and a need for anticoagulation in some of them^{24,25}.

The highlight of current technological endeavour in diabetology is the creation of a “an artificial pancreas”. The intensive care setting with patient’s energy balance under control is ideal for closed-loop system clinical testing and the results are promising also in the perioperative period²⁶⁻³¹. Nevertheless, these technologies are also invasive and expensive.

Continuous glucose monitoring systems (CGMS) with subcutaneous sensors have been used since 1999. Originally, they were designed for out-patient self-monitoring. At present, they are undergoing rapid development. There are several approved devices in common use - Guardian® REAL-Time CGMS (Medtronic), Dexcom TM Seven® Plus (DexCom) and FreeStyle Navigator® (Abbott) use enzyme-based technology; the GlucoMen (Menarini) is based on microdialysis. Each marketed device has a particular accuracy profile³².

The advantage of subcutaneous CGMS is minimal invasivity, acceptable price and continual mode of glucose monitoring.

On the other hand, there is a concern over their reliability in the acute care setting³³. Goldberg used them in a medical ICU in 2004 and found 98.7% of the paired val-

ues clinically acceptable; he evaluated CGM as a reducer of glycaemia fluctuations and a promising research tool³⁴. Others found it useful for reducing hyperglycaemic episodes³⁵. The analysis of two prospective randomized trials demonstrated clinically sufficient accuracy and safety^{36,37} even in patients on vasopressors³⁸. Some reject the use of subcutaneous sensors in the ICU setting^{39,40}.

The pioneering work in the use subcutaneous sensors in a perioperative setting was a study by Hannah Piper - in pediatric cardiac surgery. The CGMS performed well in the setting of hypothermia, inotrope use, and oedema⁴¹. Other perioperative experience is limited⁴².

In personalised medicine, the safe continuous mode of monitoring would be ideal for patients at high risk of perioperative dysglycaemia.

SUBJECTS AND METHODS

We analysed clinical and laboratory data obtained from 20 perioperative CGMS-monitored cases undergoing low extremity surgery because of vascular complications. The entry criteria were: preexisting DM or impaired glucose tolerance, planned lower extremity surgery for vascular complications and informed consent of the participant. The study was conducted in 3 centres: the University Hospital Olomouc (6 participants) and two nearby regional hospitals (Prerov, 9 participants; Kromeriz, 5 participants) in the period from June 1st, 2010 to June 30th, 2011. Ethical approval was provided by the Ethics Committee and a written informed consent was obtained from all study participants. These were 17 adults, median age 69 years, 12 (65%) were male, 9 (53%) were persons with diabetes mellitus type 2 (DM 2) treated with insulin, 5 (29 %) were persons with DM 2 treated with oral antidiabetic agents, one was a person with DM 2 treated with a combination of insulin and oral diabetic agents, one was a person with DM 2 on a diet, and one was a person with impaired glucose tolerance on corticosteroid medication. All the patients were scheduled for lower extremity surgery because of vascular complications of diabetes mellitus and/or atherosclerosis. Three of the participants were monitored repeatedly also during their reoperation several weeks after the first surgery. Altogether, 20 cases of continuous perioperative monitoring were evaluated, CGM data were collected in 71 perioperative days. The list of cases is shown in Table 1.

The Guardian® REAL-Time CGMS (Medtronic Northridge, CA, USA) and a Medtronic SOF-SENSOR™ were used. The system consists of a miniature sensor placed in the subcutaneous fat (we used the abdominal or upper arm region with respect to the planned operation), a transmitter joined to the sensor, and an external monitor wirelessly communicating with the sensor, with a signal reach of approximately 2.5 m. The glucose sensing is based on the glucose oxidase method, generating an electrical current. The values are registered every 10 s and averaged every 5 min. The resulting value is transmitted to the monitor and processed by an algorithm converting the value of glucose concentration in interstitial fluid (IF)

Table 1. List of cases.

DM type	Type of anesthesia	Type of operation (for micro/macrov- giopathy-related complications)	Duration of surgery	Glycated hemoglobin HbA1C (%)*	Percentage of glycaemia values above 15.0 mmol/L**	Hypoglycaemic events under 4.4 mmol/L**	Reoperation within 3 months	ICU stay***
DM 2, diet	Spinal anesthesia	Transfemoral amputation	45 min	4.6	0			
DM 2, insulin treatment	General anesthesia	Partial foot amputation (Chopart)	20 min	8.7	11.7		+	
DM 2, insulin treatment	General anesthesia	Foot abscess, incision and drainage	20 min	4.7	2.9			
DM 2, insulin treatment	Local anesthesia	Necrectomy of digits	20 min	4.8	1.9		+	
	Spinal anesthesia	Amputation below knee	60 min	no value	29.2		+	65 h
DM 2, insulin treatment	General anesthesia	Amputation of digits	40 min	7.4	2.8		+	
IGT, corticosteroid medication	General anesthesia	Partial foot amputation	30 min	3.6	0			
DM 2, insulin treatment	General anesthesia	Amputation of digits	20 min	15.5	49.6		+	69 h
	General anesthesia	Partial foot amputation	25 min	7.5	0			
DM 2, oral diabetic agents	General anesthesia	Amputation of digits	20 min	5.2	6.3		+	
DM 2, oral diabetic agents	General anesthesia	Partial foot amputation (Chopart)	35 min	6.3	6.7		+	20 h
DM 2, insulin treatment	General anesthesia	Amputation of a digit	20 min	4.3	0	+	+	
	General anesthesia	Foot abscess, incision and drainage	30 min	3.3	0	+		
DM 2, insulin treatment	General anesthesia	Amputation below knee	60 min	7.0	26.4		+	20 h
DM 2, oral diabetic agents, insulin treatment	Spinal anesthesia	FP bypass	195 min	7.6	24.8		+	45 h
DM 2, oral diabetic agents	General anesthesia	FP bypass	180 min	6.6	6.6	+	+	27 h
DM 2, insulin treatment		Prepared for FP bypass, MRI examination		5.2	0		+	
DM 2, insulin treatment	Spinal anesthesia	Profundoplasty	160 min	6.4	0.2			23 h
DM 2, oral diabetic agents	General anesthesia	1. Aortobifemoral bypass	240 min	4.3	6.6	+	+	42 h
	Spinal anesthesia	2. Thrombectomy, endarterectomy	120 min					
DM 2, oral diabetic agents	Spinal anesthesia	Profundoplasty	120 min	13.7	5.1			19 h

Patient 17 underwent auxiliary magnetic resonance imaging, therefore CGM data from the first 18 hours only are stated (included the night before operation, preparation for operation, e.g. fasting and preoperative infusions).

Patient 18 underwent a planned aortobifemoral bypass surgery followed by an emergency reoperation (thrombectomy and embolectomy of the bypass) in the evening on the same day.

* IFCC approved nomenclature (one-time measurement)

** CGMS data.

*** Surgical ICU immediately after the surgery, with the exception of patient K.B. in her second monitored period (rank of the case No.5) who was hospitalised in cardiac ICU on her 4. postoperative day because of a coronary ischemic event.

to the value of plasma glucose (PG) concentration. This algorithm depends on the calibration value. The monitor displays a fresh calculation of PG every 5 min. The system is capable reporting PG concentration in a limited range 2.2 - 22.5 mmol/L (39.6 - 405 mg/dL), providing up to 288 recordings per day. A major advantage is that the trends e.g. the velocity of elevation or decrease in plasma glucose, are graphically visible. Retrospectively, all registered values can be displayed. It is possible to upload the data to a computer and obtain a statistical value distribution on individual days. A useful function is an event notification (the time of events as treatments, surgical procedures or meals can be recorded). The alarms

could be set not only for reaching critical limits, but also upon anticipation of reaching a limit in a short time. In our observational study, we did not use the alarm function in order not to contribute to the patient's perioperative stress. The sensors were calibrated two times daily by the Wellion Linus glucometer (AgaMatrix, USA).

CGM was introduced on the day before surgery and continued for mostly 3 days with some exceptions. In one case the CGM was terminated prematurely because of the need for urgent magnetic resonance imaging. Some of the participants were monitored longer because of the postoperative metabolic instability.

In addition to CGM, our patients had a laboratory PG profile (a capillary blood from a the fingerprick) scheduled at 6, 11 and 17 o'clock.

During the surgery, the paired values were taken by the point-of-care PG testing by the means of Wellion Linus glucometer (AgaMatrix, USA), 20 min before the start of the surgery and then every 15 - 20 min according to a preset protocol.

The body temperature was measured before and after the surgery and none of the patients was found febrile. A standard pain management following the procedure-specific recommendations was applied in all the patients, the pain control medication was titrated according the Visual Analogue Pain Intensity Score to grade 0 - 1.

RESULTS

Applicability

In contrast to a previous study⁴¹, we did not register any electromagnetic interference (no alarm, no loss of signal) with electrocauterisation during the surgery or with other electronic devices.

The coping with CGM was different for the nursing staff of the common surgery department and for the Intensive care setting (ICU) nursing staff. The ICU staff of all three centres were able to use the CGMS independently and to fully benefit from this technology, even maintaining the sensor longer than the planned 3 days in complicated cases with marked dysglycaemia. The insulin therapy was modified by the ICU attending physician. The nursing staff of the normal surgery department were less successful in using the information provided by the CGMS sufficiently, resulting in more patients outside the safe PG ranges than expected.

Of 19 patients meeting the entry criteria, 17 agreed to take part in the study. It was their first experience of GGM for all of them. Three of them with marked perioperative dysglycaemia were offered CGM also during their reoperation, which followed few weeks after their first CGMS monitored surgery - all of them agreed.

The use of CGMS was well-tolerated by all patients, who mostly appreciated having continuous PG control. All of them evaluated the initial sensor insertion procedure as minimally painful - less than the capillary blood sampling. Younger, "computer literate" patients tested their glycaemic sensitivity to particular meals and this helped them to overcome the healing period. Older patients were more inattentive to the new technology and some of them were stressed by the occasional noise of alarm caused by loss of signal, when they forgot the monitor behind them as they left their beds.

No adverse effects were registered even in patients with infection (diabetic gangrene with fever) or those who had the sensor inserted for 5 days or longer.

Meeting the target glucose range (4.4-11.1 mmol/L) and a postoperative outcome

We evaluated the PG data collected by CGM and the outcome of enrolled patients in all 20 perioperative cases.

We found an association between degree of perioperative dysglycaemia and postoperative outcome. The patients with marked stress-induced dysglycaemia more often needed a reoperation within next 3 months.

Only 4 out of 20 cases (20%) met the criteria for the safe perioperative target glucose range (4.4-11.1 mmol/L). There was just one reoperation within 3 months needed in this group.

The group with maximal perioperative PG value in the range 11.1 - 15.0 mmol/L accounted 6 cases with 3 reoperations within 3 months.

The maximal perioperative values of PG in the range 15.1 - 20.0 mmol/L were found in 7 cases, 6 of them needed a reoperation within 3 months.

There were three cases exceeding the perioperative PG value of 20.1 mmol/L and all of them needed a reoperation within 3 months.

Accuracy

We compared the values of plasma glucose (PG) concentration referred by CGMS (n = 131) with those measured with a central laboratory analyser (a "gold standard") collected at the same time by regular capillary blood sampling (results in Table 2). The Wilcoxon signed-rank test (89 values) and paired Student's t-test (42 values) revealed no significant difference between the values of plasma glucose measured by CGM and by a laboratory analyser at 6 am, 11 am and 5 pm.

The horizontal line inside the quartile box plot represents the median (50th quartile), the bottom and top of the box are the 25th and the 75th percentiles (the lower and upper quartiles, respectively). The ends of the whiskers represent the minimum and maximum values. The outlying values are plotted as small circles, the extreme values are plotted as asterisks.

Fig. 1. The box-and-whisker plot shows the distribution of differences of plasma glucose values measured by the CGMS and the laboratory analyser (in %).

During the operation day, two glucose infusions were distributed: glucose 10% 500 mL with Humulin R 10 IU (6:30 – 8:50 am) and glucose 10% 500 ml with Humulin R 12 IU (11:30 am – 1:30 pm).

Fig. 2. K. K., M, 1947, type 2 DM. On 22. 6. 2011, profundoplasty, ilicoprofundal interposition, desobliteration of a. profunda femoris were performed under spinal anaesthesia (2.30 - 4.30 pm).

The box-and-whisker plot (Fig. 1) shows the distribution of the differences of the PG values referred by CGM and the laboratory analyser.

We correlated the values of PG concentration referred by CGM to the values obtained by the AgaMatrix Wellion Linus glucometer with respect to either the intraoperative period including 30 minutes after surgery ($n = 51$), the first postoperative day ($n = 103$) and the whole perioperative period ($n = 350$). Pearson's correlation coefficients were

$r = 0.866$ for the intraoperative period, $r = 0.903$ for the first postoperative day and

$r = 0.875$ for the whole perioperative period (data collected from 71 perioperative days).

The accuracy of the sensor values with regard to the length of its insertion was also studied. The sensor was placed for 6 or more days in 4 cases. In one of them (Case 8, see Table 1), there was a decline in accuracy during the 6th day of use (difference of PG values between the sensor and central laboratory analyser was more than 3 mmol/L).

Identification of patients profiting from CGMS

CGM is not an expensive technology and it can be used to identify patients who are at risk of more serious perioperative dysglycaemia and who would benefit from continuous PG monitoring. In our experience, the risk factors are as follows:

1. DM treated with insulin or oral antidiabetic drugs
2. Ongoing infection, critical illness or additional metabolic imbalance
3. Preoperative glycated haemoglobin HbA1c (IFCC) above 7% (ref.^{13,43-45}) or marked preoperative glycaemic variability (The interpretation of HbA1c should take into account recent blood transfusions, haemolytic processes, haemoglobinopathies etc.)
4. Corticosteroid medication

DISCUSSION

Ad I. We have some practical remarks on the feasibility of CGMS in the perioperative period. It is necessary to introduce the sensor at least 2 h before the intended monitoring. After the sensor acclimatisation in the subcutaneous tissue, the monitor requests the first calibration and immediately afterwards starts displaying the values of glycaemia.

The current disadvantage of transcutaneous CGMS in the in-patient setting is the limited reach of the transmitter signal (2.5 m) constituting complications especially during the transfer to the operation theatre. The gaps in glycaemia curves (Fig. 2 and 5) are caused by transient loss of signal when a monitor was accidentally removed from the reach of the transmitter. Improved telecommunication abilities (optimally reaching the central monitor in the nurses' room) would certainly promote CGMS applicability.

The limited range of PG values measurement (with the Medtronic Guardian® REAL-Time CGMS from 2.2

to 22.5 mmol/L) was exceeded in 3 cases of hypoglycaemia and in 6 cases of hyperglycaemia in our cohort. This limitation could be a disadvantage in certain groups of patients (e.g. in hypoglycaemia measurement of premature neonates).

The correct interpretation of CGM data is substantial. We must consider a time lag between the value of PG concentration and the glucose concentration measured in the interstitial fluid (IF) compartment. The IF glucose value could be delayed after the PG value by about 15 - 20 min (when PG concentration is on rise) and about 5 minutes (when it is descending). The time lag depends on the type of device.

We observed no adverse effects of CGMS use in our study. A small number of local complications have been described in the literature, ranging from minor complaints such as skin sensitisation to abscess formation⁴⁶. Our results are in accordance with the evidence of low incidence of side effects caused by CGMS use.

Ad II. CGMS technology constitutes a step towards a personalised medicine. We demonstrate the most typical patterns of the perioperative PG development.

Even liberal control of PG is sometimes difficult to achieve. The reasons could be increased postoperative insulin resistance, unsuccessful control of infection, and also an uncertainty of the medical staff about the safe glycaemic range given that tight glycaemic control was found to be harmful. Some of the patients suffered from too high perioperative hyperglycaemia and a most did not meet the criteria for the safe blood glucose range. In this context, the CGM output in gross could be used as an indicator of the quality of care.

Hyperglycaemia was the most common problem, we also noticed mild asymptomatic hypoglycaemic episodes in 4 cases out of 20 cases.

The most serious consequence of perioperative hyperglycaemia is alteration of the immune response (phagocytosis and chemotaxis), resulting in impaired wound healing and higher postoperative sepsis rate. The infection and hyperglycaemia create a vicious cycle. The resolution of hyperglycaemia leads to normalisation of the inflammatory response⁴⁷. Further sequelae of hyperglycaemia include increased blood viscosity, endothelial dysfunction and osmotic diuresis resulting in the loss of minerals and increased risk of dysrhythmias and ischemic events.

The most frequent patterns of perioperative glycaemia course are demonstrated in following diagrams 1. - 4. (Medtronic CareLink™ Personal Software).

1. Glycaemia peak on the day of surgery

This is a typical perioperative evolution of glycaemia (Fig. 2).

2. Persistent perioperative hyperglycaemia

Persistent perioperative hyperglycaemia is a frequent perioperative record (Fig. 3). This complicated patient developed persistent postoperative hyperglycaemia exceeding the limit of sensor measurement capability 22.5 mmol/L (405 mg/dL). The glucose control was surprisingly insufficient. He needed additional surgical proce-

Glucose 10% 500 mL with Humulin R 12 IU was distributed from 6.50 to 9.00 am before the surgery.

Fig. 3. K. J., M, 1940, type 2 DM. On 27. 4. 2011, profundoplasty and a femoropopliteal bypass were performed under spinal anaesthesia (9:45 am – 1:00 pm).

dures because of ongoing wound infection. Patient with similar glycaemic course may benefit from the novel approach, a basal-bolus insulin therapy in the perioperative period⁴⁸.

3. Tight glycaemic control with episodes of hypoglycemia

In Fig. 4, an example of tight glycaemic control with episodes of hypoglycaemia is demonstrated. Such events would be underdiagnosed by conventional intermittent PG control.

In our group of patients, hypoglycaemia was registered in 4 cases only (20%, see Table 1). No hypoglycaemia event was reported during the surgery (borderline values were registered for a short time only in the case in Fig. 5).

4. Plasma glucose variability (enhanced by preoperative infusion)

The patient in Fig. 5 had been prepared for the surgery, which was finally postponed to the next day. We suppose that his PG fluctuation was enhanced by preoperative infusions on both days.

In contrast, Fig. 6 presents the conventional PG profile of the same patient. In patients with similar high PG variability, we could be quite unaware of transient hypo- or hyperglycaemic excursions if the frequency of PG sampling is not high.

5. Hunger after the surgery

This curve illustrates a peculiar event. A patient did not adhere to the instructions given by the nursing staff and after the amputation of a digit under general anaesthesia, he consumed approximately 300g of pastry immediately after coming back from the operating theatre to the ward. The resulting glycaemia peak, explained further by this event, is shown in Fig. 7.

Participants within the safe glucose range had the lowest incidence of reoperations. However, we can pose a question “What is the chicken and what is the egg?” – maybe the sickest patients are truly so sick that their PG levels are difficult to treat. Based on these results, it was impossible to discriminate whether a dysglycaemia

Too tight glycaemic control. Glucose 10% 500 mL with Humulin R 12 IU 7:00 – 9:00 am on the day of surgery.

Fig. 4. G. J., F, 1938, type 2 DM. On 8. 6. 2011, incision and drainage of a foot abscess were performed under general anaesthesia (12:30 am – 1:00 pm).

registered by CGM is a predictor of a negative outcome (e.g. a marker of impaired metabolic balance and insufficient control of infection) or a factor directly contributing to that negative outcome (due to metabolic changes and predisposition to infection). In any event, marked perioperative dysglycemia (Fig. 3 and 5) signals the need for additional therapeutic intervention - not only change of insulin therapy, but often also a decision about antibiotic therapy, sufficient surgical control of infection, more adequate pain therapy (in our group of patients the pain therapy was adequate), stress reduction etc.

The commonly distributed preoperative glucose infusion seems to be a frequent cause of perioperative PG spikes (example in Fig. 5).

Marked PG perioperative variability as shown in Fig. 5 is generally linked with poor outcome. Analogically to perioperative hyperglycaemia, it could be a secondary sign of a generally poor condition, but it may also contribute to it.

Although the sample size was too small to prove association between degree of perioperative dysglycemia and outcome of surgery, our results confirm other studies^{4,9}.

Ad III. Our study was an observational one. It will be interesting to plan an interventional study with a control group without CGM to prove the potential benefit of CGM use on the postoperative outcome of the patients with DM. For future studies, we recommend the creation of CGM service team for surgery wards to supervise a correct calibration procedure and to help in the CGM implementation into routine nursing care. An important matching factor for the control group should be the degree of preoperative DM reflected in the glycated haemoglobin HbA1c, together with the preoperative PG variability.

The pinpoint of our study was not to ascertain the accuracy of current CGMS - we consider this question as being already solved by larger studies mentioned above³³⁻⁴¹. We focused on glycaemia trends of operated patients, on identification of frequent patterns of glycaemic reaction to stress and on the determination of eventual CGM impact on glycaemic stability in individual cases. Nevertheless we completed our observation by statistical analysis of the data which showed no statistical difference between CGMS and laboratory analyser data, and a strong correlation of CGMS and glucometer data. We found that

Glucose 10% 500 mL with Humulin R 12 IU was distributed from 7:00 to 7:45 am before the surgery.

Fig. 5. Z. A., M, 1946, type 2 DM. 24. 5. 2011, prepared for operation, given an preoperative infusion (Glucose 10% 500 ml with Humulin R 12 IU from 6:50 to 9:20 am) but the surgery was postponed. On 25. 5. 2011, a femoropopliteal bypass was performed (8.00 - 11.00 am) under general anaesthesia.

the difference between collected CGMS and glucometer data (e.g. the difference between the measurement from interstitial and capillary compartment) does not change substantially between intraoperative, postoperative and whole perioperative time. The haemodynamic changes during the surgery and anaesthesia reduced the correlation only slightly. (The plasma - interstitium delay does not influence the correlation between the results of both methods of PG measurement, while these tests do not measure the absolute deviation between them).

The Wilcoxon signed-rank test (89 values) and paired Student's t-test (42 values) revealed no significant difference between the values of plasma glucose measured by CGM and by a laboratory analyser.

The significance of our statistical results is limited by small sample.

Despite this acceptable correlation, we found occasionally greater discrepancies (more than 2 mmol/L = 36 mg/dL PG concentration) between the values of CGMS and laboratory analyser ("gold standard") in some

cases over limited periods of time. On our opinion, these inaccurate CGM was caused mostly by an improper calibration (the lack of supervising CGM team on standard wards) but we cannot rule out inaccuracies caused by local conditions in the tissue of the sensor insertion. These inaccurate measurements could cause a treatment mistake, if CGM is a stand-alone method of PG assessment.

Therefore we share a cautious conservative opinion: The CGM is useful in revealing the PG trends, alerts us in case of unexpected PG deviations (the speed of the change of PG trend indicates a need for initiating an approved laboratory test) and provides us with a complete information on the patient's daily PG range, pattern and variability but laboratory checks of single values before the treatment decision are inevitable.

Until we have a new generation of "robust, high-performance sensors", the Rice's comparison is valid: PG values estimated by a laboratory analyser are like an accurate snapshot, CGM data are like a bit blurry movie but providing us with a real-time picture⁴⁹.

For the first three days, the values of glycaemia were “falsely” unremarkable.

Fig. 6. The same patient, conventional PG daily profile, central laboratory analyser.

Glucose 10% 500 mL with Humulin R 16 IU was distributed from 7:00 to 10:00 am before the surgery.

Fig. 7. S. F., M, 1938, type 2 DM . On 17. 3. 2011, amputation of a digit (12:40 am – 13:00 pm) was performed under general anaesthesia. The patient did not follow the instructions of the nursing staff and consumed a meal immediately after the surgery.

Due to the interstitium - plasma time lag phenomenon, subcutaneous CGM could never be 100% in accordance with the laboratory analyser - but provided this delay is similar to the delay between plasma and central nervous system glucose concentration, the IF glucose concentration more realistically reflects the central nervous glucose concentration than directly measured PG⁴⁹. If this hypothesis is confirmed, it would be beneficial to display the original IF glucose concentration in addition to the calculated PG value.

The correct use of CGM promotes its accuracy. The most essential procedure is a correct calibration, with an externally gained value of PG being set to the monitor. Calibration is required twice daily, in the time when no fluctuations in PG are expected (it is incorrect to calibrate during or after the meal, during or after glucose or insulin administration etc.). In case of unexpected discrepancy between CGM and laboratory data it is good

to perform an extra calibration during the day; a more frequent calibration (4 times a day) leads perhaps to more accurate performance of the sensor⁵⁰. It is essential to calibrate with the most accurate device available, preferably with a laboratory or blood gas analyser. Our pilot study was performed on standard surgery wards without this opportunity, so we used the Wellion Linus glucometer (AgaMatrix, USA) based on technology which prevents the glucose reading to be influenced by the level of haematocrit⁵¹. None of our patients was calibrated in the state of hypoperfusion.

The performance of the Medtronic sensor is guaranteed for 6 days and may work well much longer^{52,53}. Even so a gradual decline of accuracy with the time is sometimes observed due to the biofilm formation on the sensor surface, subclinical inflammatory response to a foreign body and formation of reactive oxygen species (ROS) interfering with electrochemical sensing^{54,55}. In such case,

the sensor should be removed and replaced. We registered a progressive decline of accuracy in Case 8 (see Table 1) during the 6th day of use (the sensor was removed on the same day). The difference of PG values was more than 3 mmol/L (54 mg/dL) between the sensor and laboratory analyser. This patient had the highest preoperative HbA1c value and a high perioperative PG variability confirmed also by laboratory analyser. If this could be a factor contributing to the quicker loss of sensor function is not clear and needs further exploration.

Although the debate on CGM accuracy continues, there are some issues where continuous glycaemia monitoring is preferable. PG variability was recently found to be associated with a worse clinical outcome, and CGM is perhaps the most suitable technology for PG variability calculation. CGM could be useful in collecting the data to define the optimal glycaemia management strategies of different groups of surgical patients (with SID, with or without DM, critically ill or not, type of surgery, various populations and therapeutic strategies, etc.) and it could also help us to gain the data for comparing the influence of different kinds of anaesthesia on insulin sensitivity⁵⁶.

Ad IV. In personalised medicine, the perioperative use of CGMS could be helpful especially in cases of complicated metabolic disorders.

CONCLUSION

Although subcutaneous CGMS have accuracy limitations compared to central laboratory devices and are not applicable as a stand-alone method for intraoperative PG monitoring, they may still be helpful to individualize treatment. The CGMS technology is safe and has the potential to develop into a new standard for perioperative surveillance, contributing to a detailed investigation of the perioperative homeostasis. Further studies with a new generation of "high performance" sensors and monitors with upgraded options would be desirable to evaluate a potential benefit for keeping the patient within the safe PG range in the dynamic perioperative period.

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CONFLICT OF INTEREST STATEMENT

Author's conflict of interest disclosure: The authors state that there are no conflicts of interest regarding the publication of this article.

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