Clinical evaluation of blood glucose variability with continuous intravenous measurement in ICU patients (GLIC-study)

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Observational invasive

Summary

ID

NL-OMON40555

Source
ToetsingOnline

Brief title
GLIC3.0

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
hyperglycemia, stress diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Sint Antonius Ziekenhuis

Source(s) of monetary or material Support: Edwards Lifesciences,Edwards Lifesciences SA

Intervention

Keyword: continuous glucose measurement, critically ill patient, hypoglycemia, post-operative phase

Outcome measures

Primary outcome

Primary endpoint in this study is to evaluate the added value of continuous

intravenous measurement of blood glucose variability after cardiothoracic

surgery and during treatment at respectively, the Intensive Care Unit and

Medium Care Unit.

Study parameters in this study are calculation of:

- mean glucose (mmol/L) (per patient, per subgroup, total average)

- percentage of patients observed experiencing severe hyperglycemia (glucose >

10.0 mmol/L),

- percentage of mild hyperglycemia (glucose 6.1-10.0 mmol/L)

- percentage of mild hypoglycaemia (2.2-3.9 mmol/L)

- percentage of severe hypoglycaemia (<2.2 mmol/L)

- percentage of time out of target range (4.4 * 6.1 mmol/L)

- percentage of blood glucose CV (coefficient of variation) (in %).

Secondary outcome

-

Study description

Background summary

Critically ill patients frequently develop hyperglycemia, independent of a history of diabetes. This concept of hyperglycemia (stress diabetes) as an adaptive mechanism to stress in critical illness has been accepted for years.

Since 2001 studies showed that targeting plasma glucose levels of 4.4-6.1 mmol/L compared to acceptance of hyperglycemia significantly decreased the mortality and morbidity in post-operative cardiosurgical patients and reduced morbidity in medical ICU patients.
These Intensive Insulin Therapy (IIT) studies were performed by infusing intravenous insulin continuously. The small target range was successfully reached and maintained by a huge increase in intermittent glucose measurements and the use of extensive and difficult insulin dosing-protocols.
Despite the protocol and frequent glucose measurements in the first IIT-study, there was a significant increase in severe hypoglycaemic events (0.8% of the patients in the control group versus 5.1% in the IIT group developed a glucose < 2.2 mmol/l). Much worse was the incidence of severe hypoglycaemia in medical IIT treated ICU-patients (18.7% of the patients).
The occurrence of hypoglycaemia in critically ill patients is associated with a higher mortality.
The incidence of severe hypoglycaemic events during IIT could probably be reduced by increasing the frequency of glucose measurement during insulin therapy and / or by adjusting the target range. Recent recommendations on measurement of blood glucose and glycemic control in critically ill patients advise a suboptimal range of 4.0-10.0 mmol/L.
However, increasing the target range gives more opportunity to increase the variation in glucose levels. Recent studies show that increased glycemic variability, defined as a coefficient of variation (CV) of >20%, has a strong independent association with increased risk of mortality in patients without diabetes.

The current IIT-protocols in several ICUs prescribe continuous administration of insulin with intermittent measurement of glucose with an interval between glucose measurements up to four hours. Each patient, independent of a medical history of diabetes and independent of admission type, is treated following the same protocol. Several studies have shown that mortality in patients treated with IIT is higher in patients with a medical history of diabetes mellitus and in septic patients. Therefore the target range can differ between patients admitted to the ICU.

The GlucoClear glucose-sensor is an accurate glucose-oxidase coated sensor developed for continuous intravenous glucose measurement in ICU-patients. Recently (May 2013) the ICU nurses and doctors of the St Antonius Hospital

Nieuwegein, The Netherlands, obtained experience with this glucose-sensor (GLIC 1-study). Its accuracy is already tested and CE marking is obtained.

Subsequently (October 2013), in the context of a study, we monitored 25 ICU patients with the continuous intravenous glucose sensor, during IIT. The patients (post-operative cardiothoracic surgical-, septic- and medium care patients) were treated following the local IIT protocol (target range for glucose 4.4-6.1 mmol/L) with intermittent arterial point of care (POC) blood glucose measurements. The monitor was blinded and the data were analysed after completion of the study (GLIC 2-study).

The mean blood glucose value was 6.3 mmol/l and the mean blood glucose CV was 22.9%. 96% of the patients had blood glucose levels outside the target-range with a duration of 63% of the observed period, 32% of the patients had severe hyperglycemia (glucose > 10 mmol/L) and 44 % of the patients had hypoglycaemia (glucose < 3.9mmol/L). Despite extensive experience with IIT in critically ill patients, it remains difficult to maintain the blood glucose levels in these patients in the target-range. Almost all patients experience blood glucose levels both sides outside the target range with harmful blood glucose fluctuations.

Up till now, no study investigated the clinical implementation of ITT with continuous intravenous glucose monitoring.

Study objective

Our hypothesis is that continuous intravenous glucose monitoring is helpful in ICU patients treated with IIT to:

a) reach and maintain the glucose-target of 4.4-6.1 mmol/L sooner
b) to increase safety, by eliminating the development of hypoglycaemia
c) reducing the blood glucose CV, especially in high risk groups like sepsis patients and patients recovering on the ICU or the medium care unit (MCU) who still are insulin-resistant and start to eat
d) to reduce workload for blood glucose sampling by the nursing staff.

Future continuous glucose measurements may reduce the workload associated with frequent conventional glucose measurements. Moreover, major inaccuracy in Point Of Care (POC, arterial blood sample) measurements can be attributed to pre-analytical (sampling and handling of samples) variables which are expected to be irrelevant when using the more accurate GlucoClear sensor.

The patients will probably reach the target range sooner while measuring the blood glucose levels continuously compared to intermittend glucose measurements. Especially in hyperglycaemic keto-acidotic diabetic patients, continuous glucose measurement can be a valuable tool to reach normoglycemia soon and safe, without development of severe hypoglycaemia.

Additional questions to be answered could be if there is a difference in glucose variability between diabetic and non-diabetic patients and if this could be related to postoperative morbidity or mortality. Future research of fully automated closed loop insulin dosing guidelines, to reach the blood glucose target range and without potentially harmful hypoglycemia, will be challenging and help to improve patient care.

The objective of this study is to improve the implementation of IIT in critically ill patients using continuous intravenous blood glucose monitoring. Improvement is defined by preventing hypoglycaemia (glucose < 3.9 mmol/L), reducing the blood glucose CV to less than 20% and reducing the percentage of patients experiencing hyperglycemia after the target-range of 4.4-6.1 mmol/L is reached.

Study design

Non-randomized, prospective, observational study to evaluate the added value of continuous intravenous glucose measurement by GlucoClear.
No extra blood samples will be collected. Values of the blinded glucose trend will be compared with the local IIT protocol glucose samples afterwards.
During the non-blinded part of the study, comparison with POC measurements is no longer required.
Glucoclear measures automatically continuously (5 minutes-interval) maximally 72 hours.

Patients admitted to the ICU with severe sepsis: After admission to the ICU and blood glucose levels are twice below 4.4 mmol/L or above 6.1 mmol/L the patient receives a peripheral intravenous catheter. Subsequently, the sensor for continuous glucose measurement will be placed into the catheter. Subsequently, 1 or 2 IE/ hour of insulin infusion will be started intravenously using another venous access. The continuous glucose measurement starts after positioning the sensor and calibration time of 20 minutes and will be continued for at least 8 and maximally 72 hours in the ICU. For patients who at the ICU and start to eat or are transported to the MCU and start to eat within 72 hours after placement of the GlucoGlear, the GlucoClear remains attached and the measurements and insulin infusion rate will be performed.

Patients admitted to the ICU after cardiothoracic surgery: Patients undergoing a cardiothoracic surgical procedure and are expected to stay in the ICU post-operatively for at least two days will be included in the study.
Postoperatively the GlucoClear will be attached and calibrated.
The target range is supposed to be 4.4-6.1 mmol/L. After surgery the patient will be transported to the ICU and intensive insulin therapy will be implemented. In the ICU insulin will be administered continuously, without administration of a bolus.

Patients who are not yet included for GlucoClear which are transported to the

MCU and expected to stay at the MCU for three days and develop hypoglycaemia (glucose < 4.4 mmol/L) or hyperglycemia (glucose > 6.1 mmol/L) twice within 30 minutes are included for continuous glucose monitoring with GlucoClear and insulin treatment.

Every 5 minutes a 20 microliter blood sample will be obtained automatically into the catheter, blood glucose level measured by the sensor and the sampled blood will be infused back automatically intravenously through the same catheter. The obtained measurements by GlucoClear will be visible on the monitor immediately for nurses and medical staff. The local IIT-protocol with intermittent measurements is a nurse driven protocol.

Therefore, the study IIT-protocol with continuous measurements will also be nurse-driven. The nurses are instructed to evaluate the glucose-trend each 20 minutes (after 4 measurements) to decide if insulin dose has to be changed (the obtained blood glucose level and the change of insulin-infusion rate is recorded in Metavision and filled in a form for later analysis. The nurses are allowed to change the insulin-infusion rate for reaching the target range, by changes of 0.1-2.0 IE themselves. The nurse is not allowed to administrate a bolus of insulin. In situations where the glucose-levels are extreme high or when there is no response, the intensivist will be consulted.

The main goal is to reach the target-range of 4.4 - 6.1 mmol/L as soon as possible and to maintain the glucose level in the target-range by changing the insulin-infusion rate. If the medical staff is not confident with the sensor readings or there are too much missing values, blood glucose measurements by POC or bloodgas (both bloodsamples from the arterial line) are allowed. If the sensor is not measuring correct or there is a dysfunction of the sensor which is not recovered within one hour, a new sensor will be placed or the observation will be aborted and the former IIT-protocol with intermittent measurements will be followed.

The study ends when a patient is transported to the ward, or after 72 hours, or when the GlucoClear is not measuring continuously (missing values) or if continuous monitoring is still not possible after replacement of the sensor and/or catheter.

Study burden and risks

All study patients have an extra peripheral venous catheter for continuous glucose measurement.

Local phlebitis of the intravenous catheter for the sensor for the continuous glucose measurements could be an adverse event. In that case we finish the measurements and the catheter will be removed. The risks associated with this study are not greater than the inherent risks associated with the procedure

involving the introduction of any venous catheter.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Age of 18 years or older, surgical or medical patients admitted to the ICU or MCU with a planned stay at the ICU of at least 8 hours.

Exclusion criteria

No informed consent
Contra-indication or allergy for heparin

Glucose in targetrange (4.4-6.1 mmol/L)
Pregnancy
Difficult to place a peripheral intravenous catheter

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-09-2013
Enrollment:	60
Type:	Actual

Medical products/devices used

Generic name:	GlucoClear
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	30-08-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	07-05-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

(Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL44987.100.13