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Continuous subcutaneous glucose monitoring. A descriptive study of its use in critical patients

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Introduction:

Glycemic control disturbances, including type 1 and 2 diabetes, are increasingly prevalent in the general population, with estimates suggesting that this trend will persist for at least the next 20 years (1, 2). Critically ill patients are particularly predisposed to glycemic disturbances due, among other factors, to stress, fasting, infections, and administered treatments (3).

Hyperglycemia is detrimental to critically ill patients. Sustained high blood glucose levels lead to immunosuppression, hindering leukocyte function, reducing phagocytic capacity, and disrupting complement function. Furthermore, hyperglycemia enhances proinflammatory mechanisms and oxidative stress. Hemodynamic management is also affected, resulting in endothelial dysfunction and osmotic diuresis, promoting dehydration, electrolyte imbalances, and tissue hypoperfusion (4). For this reason, most current recommendations for glycemic control in critically ill patients advise treating hyperglycemia with insulin when blood glucose exceeds 180 mg/dL (5).

However, the ideal blood glucose range for maintaining our patients is still a subject of debate. Despite knowing that hyperglycemia is harmful, its treatment carries a high risk of hypoglycemia. Severe hypoglycemia (glucose <40 mg/dL) increases the risk of death from any cause in critically ill patients by more than threefold (6). The incidence of hypoglycemia in critically ill patients varies widely depending on the patient type and the protocol used for hyperglycemia control, but it is generally estimated that between 3% and 20% of critically ill patients may experience severe hypoglycemia during their hospitalization (7). On the other hand, hypoglycemia can be easily prevented or treated in hospitalized patients through the infusion of glucose solutions if correctly identified (8).

In recent years, the use of continuous subcutaneous glucose monitoring (CGM) sensors has revolutionized clinical practice in non-hospitalized diabetic patients (9). Subcutaneous glucose is directly related to capillary and arterial blood glucose (10), so changes in blood glucose concentration are transmitted to subcutaneous tissue within the next 5 to 10 minutes (11). CGM in critically ill patients has been shown to significantly reduce the incidence of hypoglycemia, mortality, and glycemic variability compared to standard practice (12).

Given the current evidence, a guide for the use of CGM sensors in critically ill patients undergoing insulin treatment has been developed in the Intensive Care Unit (ICU) of HLA Moncloa University Hospital. The main objective of this guide is to attempt to reduce episodes of severe hypoglycemia in these patients. The guide has been in use since May 2023 (ANNEX 1).

The primary utility of these sensors in critically ill patients lies in detecting patients at risk of experiencing hypoglycemia, which the investigators could consider as potential hypoglycemic events. However, to the best of our knowledge, there is currently no unified clinical practice regarding the use of these devices in critically ill patients. It is not possible to find clinical practice guidelines or recommendations for the thresholds for detecting potential hypoglycemic events or studies describing the characteristics of these events.

Therefore, this study aims to determine the cumulative incidence over the admission period and the incidence rate of potential hypoglycemic events (defined as subcutaneous glucose <80 mg/dL detected by CGM) occurring in patients admitted to the ICU at HLA Moncloa Hospital during a four-year follow-up. Additionally, it aims to describe the occurred hypoglycemic events, the type of patients using the CGM sensor, and the actions derived from the detection of potential hypoglycemic events.

Hypothesis and Objectives:

Hypothesis: It is expected that the risk of potential hypoglycemia in critically ill patients undergoing insulin treatment is 20% (7), and that measures will be taken in all patients with potential hypoglycemia to verify and, if necessary, prevent actual hypoglycemia.

Objectives:

Primary Objective:

- Determine the cumulative incidence or risk of potential hypoglycemia during ICU admission (cases of potential hypoglycemia/number of patients x 100) and the incidence rate (cases of potential hypoglycemia/1000 x patient x hour) in critically ill patients undergoing insulin treatment using CGM sensors. Potential hypoglycemia will be considered when the CGM sensor alerts for low glucose (glucose <80 mg/dL).

Secondary Objectives:

- Determine the incidence of severe (glucose <40 mg/dL), moderate (glucose between 40 and 55 mg/dL), or mild (glucose between 56 and 70 mg/dL) hypoglycemia (cases of hypoglycemia/number of patients x 100) during ICU admission and the incidence rates (cases of hypoglycemia/1000 patients x hour) in critically ill patients undergoing insulin treatment using CGM sensors.
- Determine the percentage of false potential hypoglycemia alerts, defined as alerts for potential hypoglycemia that do not correspond to low capillary glucose values (glucose <90 mg/dL).
- Describe the type of patients in the ICU who are fitted with a CGM sensor in our unit.
- Describe the glycemic profile of critically ill patients undergoing insulin treatment: (Maximum glucose, minimum glucose, average glucose, glycemic variability, time in range, Hb A1c, diet used, insulin requirement, insulin protocol employed).
- Describe the actions taken by healthcare personnel following a potential hypoglycemia alarm (administration of intravenous glucose (IV) glucosmon 50% in ml, administration of IV glucose glucosmon 33% in ml, initiation of IV glucose infusion at 5% ml/h, IV glucose infusion at 10% (ml/h), among others).
- Describe the theoretical cumulative incidence of potential hypoglycemia with alternative thresholds of 70, 75, 85, or 90 mg/dL.

Materials and Methods:

Design: This is a single-center, observational, descriptive, longitudinal, and prospective study.

Setting and Study Population: The study will be conducted on patients admitted to the Intensive Care Unit (ICU) of Hospital HLA Moncloa over a period of four years.

Inclusion Criteria:

- Patients admitted to the ICU, undergoing insulin treatment, and with a placed Continuous Glucose Monitoring (CGM) sensor.
- Adults aged 18 and above.
- Patients who provide voluntary consent to participate in the study (Annex 2). If the participant is not in full physical or intellectual capacity to provide their signature on the informed consent, the investigator in charge will request consent from their direct family member or the person legally designated to make decisions on their behalf in health matters. This measure is taken to ensure the participant's rights are respected and to maintain the integrity of the consent process, even in situations where their decision-making capacity may be compromised.

Exclusion Criteria:

- Patients from whom information about CGM cannot be obtained due to technical reasons.

Sample Size:

It is expected that around 20% of patients admitted to the ICU may develop potential hypoglycemia during their stay. Based on this, it will be necessary to include 246 patients to estimate the cumulative incidence with a precision error of 5% and a confidence level of 95%. It is estimated that approximately 60 patients per year (5 patients/month) will meet the inclusion criteria, so the study is planned to last for 4 years. Annual interim analyses will be conducted, describing the cumulative incidence and incidence rate (along with their respective confidence intervals to assess the precision error of interim estimates) for the total number of patients included up to that point.

Procedures:

1. All patients admitted to the ICU and eligible for the study will be informed about it, and their informed consent will be obtained.
2. If they agree to participate, they will ensure compliance with the inclusion criteria. Therefore, they must have a continuous glucose monitoring (CGM) sensor placed according to the detailed instructions in ANNEX 1.
3. Patients will receive treatments according to the center's usual clinical practice and the criteria of their responsible physician based on the patient's characteristics in each case.
4. The device records glucose readings every 5 minutes, automatically storing the information.
5. If the device detects potential hypoglycemia at any time, healthcare personnel will act according to the device placement guide (ANNEX 1), detailing the procedure to follow, and if confirmed, it will be corrected based on the responsible physician's criteria.
6. At the time of discharge or patient exitus, the principal investigator will review the patient's medical history to create a pseudonymized database that includes patient study variables, treatments, ICU stay duration, and continuous glucose monitoring records. This information will be stored for 5 years on the hospital intranet server alongside other confidential information from the ICU at Hospital HLA Moncloa.

Alarms:

Alarms will be set using the Freestyle Libre 2 sensor reader in a similar manner for all patients.

- Low glucose alarm (subcutaneous glucose <80 mg/dL) After the alarm is triggered, capillary, arterial, or venous glucose will be checked, and actions will be taken according to the standard protocol of the ICU at Hospital HLA Moncloa.

Definitions of Hypoglycemia:

1. Potential Hypoglycemia:

- Definition: Any subcutaneous continuous glucose measurement below 80 mg/dL, confirmed by checking capillary, arterial, or venous blood glucose values up to 90 mg/dL (a margin of 10 mg/dL difference between subcutaneous glucose and blood glucose will be allowed to confirm hypoglycemia).

2. Severe Hypoglycemia:
    - Definition: Any glucose measurement below 40 mg/dL, whether in capillary, arterial, or venous blood.
3. Moderate Hypoglycemia:
    - Definition: Any glucose measurement between 40 and 54 mg/dL, whether in capillary, arterial, or venous blood.
4. Mild Hypoglycemia:
    - Definition: Any glucose measurement between 55 and 69 mg/dL, whether in capillary, arterial, or venous blood.
5. False Hypoglycemia:
    - Definition: Any subcutaneous continuous glucose measurement below 80 mg/dL that is ruled out by checking capillary, arterial, or venous blood glucose values above 90 mg/dL.

Capillary, Arterial, and Venous Glucose:

- Critically ill patients typically undergo glucose determinations multiple times throughout the day and in response to specific symptoms (dizziness, fatigue, weakness, headaches, confusion, speech alterations, blurred vision, seizures, and coma). These measurements may include capillary glucose at the bedside, arterial blood gas analysis, or laboratory-based analysis of arterial or venous blood.
- The results of all glucose determinations performed on the patient will be systematically recorded. This approach will capture the incidence and incidence rate of mild, moderate, and severe hypoglycemia occurring during the hospitalization.

Variables:

- Patient ID
- Date of ICU admission
- Date of ICU discharge
- Date of sensor placement
- Date of sensor removal
- Age
- Reason for admission:
    - Depression of consciousness level and other neurological disorders
    - Acute coronary syndrome
    - Cardiac rhythm disturbances
    - Cardiopulmonary arrest
    - Heart failure/cardiogenic shock

    - Hypovolemic shock
    - Sepsis/septic shock
    - Shock of other etiology
    - Respiratory failure
    - Renal failure and metabolic disorders
    - Intoxications
    - Head trauma
    - Other traumas without traumatic brain injury
    - Monitoring and postoperative surveillance
    - Monitoring and surveillance of non-surgical procedures
    - Other unspecified medical or surgical diseases
- Type of admission:
    - Urgent
    - Scheduled
    - Unknown
- Type of patient:
    - Medical
    - Surgical
    - Unknown
- Origin:
    - Operating room
    - Emergency
    - Conventional hospitalization
    - Other areas of the hospital
    - Another hospital
- Status at ICU discharge:
    - Alive
    - Lethal exitus
- Hypertension (yes/no)
- Diabetes Mellitus (yes/no)
- Dyslipidemia (yes/no)
- Current smoker (yes/no)
- Current ex-smoker (yes/no)
- Hb A1c at admission
- SAPS3 at admission
- Number of potential hypoglycemic events
- Number of severe hypoglycemic events
- Number of moderate hypoglycemic events
- Number of mild hypoglycemic events
- Number of false hypoglycemic events
- Continuous subcutaneous glucose values (recorded every 5 minutes)
- Maximum glucose (median ± IQR or mean ± SD)
- Minimum glucose
- Average glucose
- Glycemic variability
- Time in range
- Diet used

- Insulin requirement
- Action taken for hypoglycemia:
    - Administration of intravenous glucose (IV) glucosmon 50% in ml
    - Administration of IV glucose glucosmon 33% in ml
    - Initiation of IV glucose infusion at 5% ml/h
    - IV glucose infusion at 10% (ml/h)
    - Other
- Insulin protocol used:
    - Modified from Brown et al. (ANNEX 3)
    - Other

Statistical Analysis Plan

To describe the sociodemographic and clinical characteristics, as well as the glycemic profile of patients, qualitative variables will be summarized using absolute and relative frequency (n and %). For quantitative variables, the normality will be assessed (using Shapiro-Wilk tests), and mean ± standard deviation (SD) or median and interquartile range [Q1, Q3] will be calculated to summarize the data.

The cumulative incidence (risk) and the incidence rate of potential hypoglycemia (defined by the continuous glucose monitoring system as <80 mg/dl) during the ICU stay will be calculated. Additionally, the cumulative incidence or incidence rate of mild, moderate, and severe hypoglycemias will be determined. For each of these epidemiological measures, a 95% confidence interval (CI) will also be calculated. The proportion of false hypoglycemias and the proportion of hypoglycemias overlooked by the continuous glucose measurement system, along with their corresponding 95% CIs, will be determined. The cumulative incidence and incidence rate of potential hypoglycemias will also be calculated using alternative thresholds (70, 75, 85, or 90 mg/dL). Statistical analyses will be performed using the STATA BE v.14 software (StataCorp) with a significance level of 5%.

Limitations

This is a single-center study, and other units may have different protocols for surveillance, target glucose range, prevention, or treatment of hypoglycemias, or admit patients with baseline characteristics different from those in this sample. Therefore, the conclusions of this study may not be applicable to other units.

Ethical and Legal Aspects

This study will be conducted in accordance with the current legislation. Both researchers and healthcare personnel at HLA Moncloa University Hospital will adhere to strict confidentiality in accessing, collecting, and processing data in the databases, while also committing to strict compliance with relevant legislation: Law 41/2002, of November 14, regulating the autonomy of the patient and the rights and obligations regarding clinical information and documentation; Organic Law 3/2018, on personal data protection and guarantee of digital rights; and Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016,

regarding the protection of individuals concerning the processing of personal data and the free movement of such data, repealing Directive 95/46/EC (General Data Protection Regulation).

All information obtained will be de-identified, pseudonymized, and anonymized from personal information before leaving the hospital network, making it impossible to identify any individual through such information. Investigators use the terms "de-identified" and "pseudonymized" interchangeably. The Health Insurance Portability and Accountability Act (HIPAA) defines de-identified information as information "for which there is no reasonable basis to believe it can be used to identify an individual." The General Data Protection Regulation of the EU (2016/679) defines "pseudonymization" as "the processing of personal data in such a manner that the data can no longer be attributed to a specific data subject without the use of additional information." Anonymized data constitute information that is not related to an individual and from which no one can be identified; such data are not subject to data protection and privacy laws.

Schedule

	January 23	September 23	November 23	September 27	October 27	November 27
Protocol Study Drafting						
HLA Moncloa Hospital Permissions						
Presentation to CEIm (Ethics Committee)						
Recruitment						
Article Drafting						
Statistical Analysis						
Submission of Final Article						

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