Hyperglycemia in nondiabetic patients during the acute phase of stroke

Hiperglucemia en no diabéticos durante fase aguda del ictus

Daniel Agustin Godoy, Caridad Soler, Walter Videtta, Luis Castillo Fuenzalida, Jorge Paranhos, Marcelo Costilla, Gustavo Piñero, Manuel Jibaja, Leonardo Jardim Vaz de Melo on the behalf of LABIC (Latin-American Brain Injury Consortium)

ABSTRACT

Objective: To determine patterns of hyperglycemic (HG) control in acute stroke. **Methods:** Anonymous survey through Internet questionnaire. Participants included Latin-American physicians specialized in neurocritical care. **Results:** The response rate was 74%. HG definition varied widely. Fifty per cent considered it when values were >140 mg/dL (7.8 mmol/L). Intravenous (IV) regular insulin was the drug of choice for HG correction. One fifth of the respondents expressed adherence to a protocol. Intensive insulin therapy (IIT) was used by 23%. Glucose levels were measured in all participants at admission. Routine laboratory test was the preferred method for monitoring. Reactive strips were more frequently used when monitoring was intensive. Most practitioners (56.7%) monitored glucose more than two times daily throughout the Intensive Care Unit stay. **Conclusions:** There is considerable variability and heterogeneity in the management of elevated blood glucose during acute phase of stroke by the surveyed Latin-American physicians.

Key words: cerebral infarction, cerebral hemorrhage, hyperglycemia, insulin, Latin America.

RESUMEN

Objetivo: Determinar patrones de control de hiperglucemia (HG) en el ictus agudo. **Métodos:** Encuesta anónima, mediante cuestionario vía Internet. Los participantes incluyan médicos latinoamericanos especializados en cuidados neurocríticos. **Resultados:** Las encuestas fueron respondidas por el 74% de los convocados. Las definiciones de hiperglucemia fueron variadas. El 50% de los que respondieron consideran HG cuando glucemia >140 mg/dL (7.8 mmol/L). Insulina regular intravenosa fue la droga de elección para su control. Solo la quinta parte de los encuestados manifestaron adherencia a un protocolo. El 23% emplea el régimen insulínico intensivo (TII). Glucemia fue obtenida a la admisión a la Unidad de Terapia Intensiva (UCI) por el total de los participantes. Test rutinario de laboratorio fue el método preferido para la monitorización. Tiras reactivas fueron utilizadas con mayor frecuencia cuando se aplicó monitoreo intensivo. El 56.7% monitoriza glucemia más de dos veces al día durante la estadía en UCI. **Conclusiones:** Existe una considerable variabilidad y heterogeneidad en el manejo de la hiperglucemia durante la fase aguda del ictus entre los médicos latinoamericanos encuestados.

Palabras-Clave: infarto cerebral, hemorragia cerebral, hiperglucemia, insulina, Latinoamérica.

Hyperglycemia (HG) is common in nondiabetic patients during the acute phase of ischemic and hemorrhagic strokes[1-5]. Reported incidence averages 40%. The pathophysiology of HG in these patients is multifactorial[6-10]. Some experimental studies have demonstrated that HG contributes to brain damage through different mechanisms: increasing blood brain barrier (BBB) permeability[11], provoking cerebral edema[11], and promoting release of inflammatory mediators[3,9,11]. An additional mechanism of injury included ischemia, mediated by vasoconstriction and microcirculation thrombosis[3,11].

The prognostic value of HG has been extensively evaluated; however, to date, it is not clear whether HG directly contributes to a worsening outcome, or whether it just represents a surrogate marker of the severity of the stroke[3,6,11]. The management of HG in this setting is still controversial and varies worldwide[11,12].

The goal for optimal glucose management in critically ill patients has been a matter of debate for several years. Some years ago, van den Berghe et al.[13] reported promising results in terms of morbidity and mortality in surgical patients with intensive insulin therapy (IIT) directed to maintain blood glucose levels between 80 to 100 mg/dL. However, the same investigators could not replicate these results in medical patients[14,15]. Meanwhile, hypoglycemia and early variability in blood glucose have been found to be independently associated with increased mortality in Intensive Care Unit (ICU) patients[16].

Latin-American Brain Injury Consortium (LABIC).

Correspondence: Daniel Agustin Godoy; Neurointensive Care Unit, Sanatorio Pasteur; Chacabuco 675. (K4700); Catamarca - Argentina; E-mail: dagodoytorres@yahoo.com.ar

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NICE-SUGAR is the largest study assessing IIT in critically ill patients[17]. There was no benefit across several predefined endpoints[17]. A recent meta-analysis incorporating the results of NICE-SUGAR concluded that IIT significantly increases the risk of hypoglycemia, without conferring a survival benefit[15].

The safety and efficacy of HG aggressive control in acute brain diseases have not been proven[11]. Modest degrees of hypoglycemia or even low-normal blood glucose levels induce the production of markers of cerebral metabolic failure[18,19].

The optimal management of HG in patients with acute stroke remains to be established. In Latin American countries, the practices for HG control in stroke patients are not well-known. For these reasons, we developed a survey in order to define current practice as a first step towards the design of future large-scale multi-center studies.

METHODS

Survey design

An anonymous survey, focusing on blood glucose control in patients with acute ischemic and hemorrhagic stroke, was developed and provided via Internet after its approval by the Scientific Committee of the Latin-American Brain Injury Consortium (LABIC). The invitation to participate was sent by e-mail. Participants were advised that the consent was implied if the respondents answered the questionnaire.

The survey was developed by neurocritical care physicians with great experience in the treatment of acute stroke patients. It was then revised by a team of external experts from other regional societies, who were blinded about other aspects of the study. The reviewers added some comments and suggestions, which provided a better understanding of the questions. The questionnaire was initially tested in four different ICUs. Ambiguous or insufficiently clear questions were reformulated.

Finally, the questionnaire and the survey protocol were approved. The invitation to participate in the survey was sent to 106 institutions in 13 Latin-American countries: Argentina, Brazil, Bolivia, Chile, Colombia, Cuba, Dominican Republic, Ecuador, Mexico, Panama, Paraguay, Peru, and Uruguay.

Only practitioners who were members of LABIC received the invitation. Three reminders were sent. After one month, it was considered that the survey was completed. The respondents entered their answers directly into the web-based survey database. As the questionnaires were anonymous, if any of them had skipped a question, no reminders were followed asking the respondent to complete it.

The survey had 17 questions to answer. The response method was multiple-choice in 13, whereas the "option to complete" was used in the remaining questions or in the topic "other" in the multiple-choice method. Firstly, the questionnaire addressed some questions related to type of ICU: general ICU or specialized neurocritical care unit; private or public institution, academic or not and number of beds. This was followed by questions about opinion concerning the relevance of the glycemic control during stroke, and definition of HG utilized. It also comprised different aspects of blood glucose control: threshold to initiate treatment, availability of a protocol for the management of HG, guidelines for insulin administration, nutritional support during glycemic control, opinions regarding IIT, blood glucose monitoring, duration of insulin treatment, and approach to diabetic stroke patients.

Definitions

The term blood-glucose management refers to active interventions used to modify blood-glucose levels. When insulin was administered, two practice models were considered: a reactive, if sliding scale regimens were used to correct changes once they occurred; and a proactive, if regimens were started to maintain blood-glucose levels according to pre-established therapeutic ranges[3].

IIT was defined as blood-glucose control with IV continuous insulin, aiming at keeping tight blood glucose targets between 80 to 110 mg/dL (4.4-6.1 mmol/L)[13].

Data management and statistical analysis

Data are descriptively presented as percentages according to the website provided survey. Further statistical analysis was not performed because of the merely descriptive nature of the survey.

RESULTS

Rate of response

Of the 106 invited institutions, 74 surveys (69.8%) were completed (one per each institution). All the signed countries were represented in the survey.

Description of participating institutions

The first question of the survey, related to the profile of ICUs, was answered by all the respondents. Sixty-seven units were general (90.5%) and only 9.4% (7/74) were specialized neurointensive care units. 52.7% (39/74) of units had public domain, while 47% belonged to private. Only 35 units (47.2%) were also research centres and 15 ICUs (20%) were general units in public hospitals.

Concerning the number of beds, 21% had less than 10, 55% had between 10 and 20, and 24% had more than 20 beds.

Relevance of HG in the management of stroke patients

The management of HG was considered essential by 81.08% of the respondents (60/74). One of them did not

answer this question, and the rest, 17.5% (13/74), considered this topic of relative importance.

Definition of HG

The definition of HG for nondiabetic patients during the acute phase after a stroke varied considerably. Different cut-off points were identified for the definition of HG: 52.7% considered it present when blood glucose levels exceeded 140 mg/dL (7.8 mmol/L); 30% placed the threshold at 110 mg/dL (6.1 mmol/L), while the remaining 18% used various other cut-off values (Fig 1).

In only 50% of cases, the definition of HG coincided with the threshold used for starting insulin therapy.

Blood glucose control

Insulin was the only drug used for blood glucose control by 98.6% of the respondents. The preferred administration method was intravenous (68.9%), followed by the subcutaneous (SC) route in 21.6%. Other routes of administration or combinations of them (SC/ intramuscular – IM, or IV/IM) were also found in a smaller proportion. Two respondents declared not using insulin and one utilized only parenteral hydration when HG was present.

Models for insulin dosing and blood glucose target varied widely: 51% preferred the reactive mode, while 33.3% applied proactive insulin regimen. In the latter group, the most frequent target of blood glucose level was between 120 to 150 mg/dL (6.6 to 8.3 mmol/L), as seen in Fig 2.

IIT was used only by 21.6% of those who advocated for the proactive regimen.

The reasons for not using IIT were in order of frequency: risk of hypoglycemia, too laborious a procedure, and lack of evidence of its usefulness.

There were also different beliefs concerning nutritional support in HG stroke patients. 89% considered necessary to modify nutrition when HG was present, 48.6% agreed with early nutrition but with modifications of caloric input, 12% preferred not to start nutrition until the clinical situation was stable, and 24.3% introduced specific nutrients for diabetic patients.

All the respondents agreed on early feeding by the enteral route.

Blood glucose levels monitoring

In the majority of the ICUs, the timing of glycaemia determination was unclear and/or highly variable. Measurement of blood glucose levels was only performed according to a strict protocol in 23% of the ICUs. All the surveyed physicians determined glucose levels at admission, and at least once a day thereafter. A total of 74% measured blood glucose at least twice a day. Blood glucose determination by a routine laboratory test was the preferred method when it was performed fewer times, whereas reactive strips were preferred when the monitoring was more intensive (four or more times per day), as in Fig 3. Among practitioners favoring a proactive treatment regimen, 83% monitored blood glucose two to four times a day and the remaining 17% did so more frequently four to six times a day.

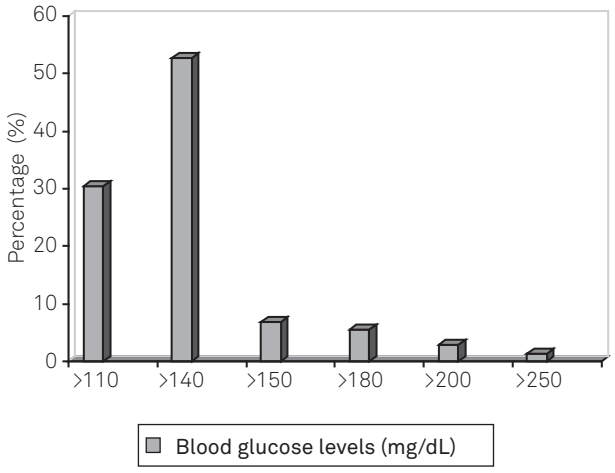


Fig 1. Variability of blood glucose levels utilized to define hyperglycemia.

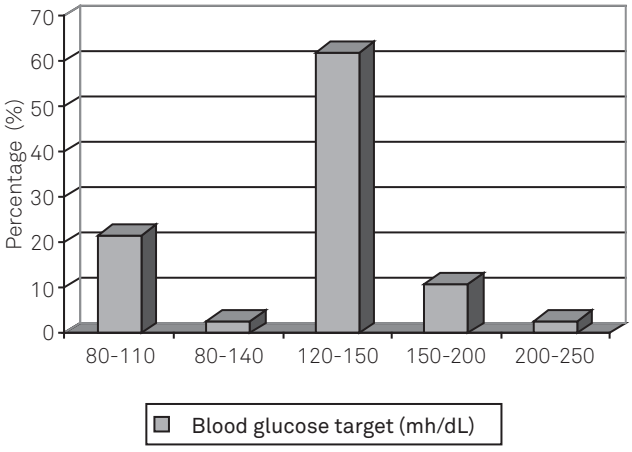
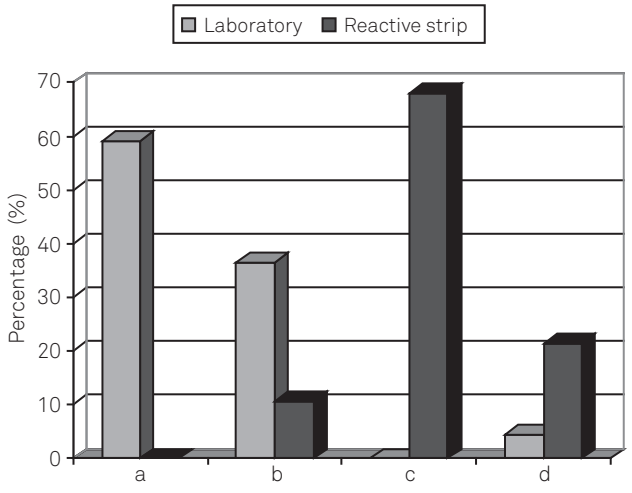


Fig 2. Blood glucose levels target in patients with proactive regimen.



Frequency of monitoring (times a day): a) 1; b) 2-4; c) 4-6; d) >6.

Fig 3. Methods of glucose levels monitoring.

Regardless of the target used, when the preferred regimen was the proactive one, monitoring of glucose levels was intensive in all cases and varied according to each institutional protocol.

Duration of blood glucose levels control

The duration of blood glucose monitoring also varied among the surveyed ICUs. 57% of the respondents (42/74) maintained glycemic control only during ICU stay, whereas 12% during the initial 48 hours, another 12% until hospital discharge and the remaining 14% maintained it during the first week after stroke onset (Fig 4). Five per cent of the respondents did not answer this question.

DISCUSSION

LABIC is a nonprofit entity founded in Rosario, Argentina, in October, 2003 by Latin-American professionals, with special interest and dedication to neurocritical ill patients. The main aim of the consortium is conducting research and educational activities involving training of professionals in the field of neurointensive care, thus developing and disseminating recommendations and guidelines for the management of different acute brain diseases, according to the possibilities and limitations of regional practices. LABIC encourages cooperation with other brain injury consortia, foundations or associations around the world. Developing a clinical practice guideline is a complex process that involves a series of necessary steps. One of the first steps must be acquiring knowledge of current practice models through the conduction of surveys[20,21].

To our knowledge, this is the first survey in Latin America directed to determine preferences and practices for the management of elevated blood glucose levels in nondiabetic acute stroke patients. Previous surveys in other parts of the world have elucidated several aspects of glycemic control, but in adult and pediatric general ICU populations[22,23].

While the majority of respondents consider this topic essential for the management of this patient population, definitions, treatment modalities and targets varied considerably.

Half of respondents considered 140 mg/dL (7.8 mmol/L) to be the ideal threshold for defining HG and initiating corrective therapy, but the response of the other half showed considerable variations, for example: HG could be defined one way (e.g. 150 mg/dL, 8.3 mmol/L), however the treatment was only started at higher values (200 mg/dL, 11.1 mmol/L).

HG in critical illness still defies a clear and homogeneous definition. A technical review written by the Diabetes in Hospitals Writing Committee of the American Diabetes Association (ADA)[24] classified patients into three groups: those with known diabetes, those with newly diagnosed diabetes, and those with hospital-related HG. However, this classification has limited utility in neurocritical care units, because it needs follow-up information that is not available during the acute phase of the disease. The proposed definition for hospitalized patients with stress HG[24] without evidence of previous diabetes was fasting glucose >140 mg/dL (>7.8 mmol/L), or random glucose >200 mg/dL (>11.1 mmol/L).

Concerning the therapy, insulin was the choice for the majority of the respondents, with the IV route being used by over two thirds of the respondents. Half of them preferred correction, based on the results of monitoring (reactive), and one third made use of a proactive scheme, using different targets, between 120 to 150 mg/dL (6.6 to 8.3 mmol/L). Only 16% used IIT and near to one fifth of respondents showed adherence to a protocol or guidelines, reflecting the wide variability in practices of monitoring and treating HG in this patient population among the surveyed centers

It is well-known that acute and persistent HG is associated with worse outcomes in patients with critical brain injury[3,11]. However, the lowest safe blood glucose level in neurocritical patients has not been defined yet.

The brain is very sensitive to fluctuations in blood glucose levels, and the acutely injured brain may have even greater susceptibility[11].

In fact, studies using cerebral microdialysis in patients with traumatic brain injuries have documented "metabolic crises", which are characterized by the increase in glutamate, and lactate/pyruvate ratio (markers of cellular distress and impending energy failure), along with reduction in the extracellular level of glucose in patients treated with IIT – target blood glucose of 90 to 120 mg/dL (4.97 to 6.63 mmol/L) –, even in the absence of serum hypoglycemia[18,19].

The threshold to begin insulin therapy was not well-determined, but some evidence suggests that the association of HG with poor outcomes starts at a level of 150 to 160 mg/dL (8.29 to 8.84 mmol/L)[4,18,19,25]. Hence, treatment of HG should be performed cautiously in these patients using validated insulin infusion protocols based on frequent glucose monitoring.

Recently, American and European associations have updated new recommendations about blood glucose management in acute phase of ischemic and hemorrhagic stroke[26-28]. The American Heart Association (AHA) recommends maintaining blood glucose levels under 185 mg/dL (10.3 mmol/L) and suggests the possibility of an additional benefit if glycaemia is maintained below 140 mg/dL (7.8 mmol/L), Class IIa, level C[26,27]. On the other hand, European guidelines recommend treating glycaemia values exceeding 180 mg/dL (10 mmol/L), level IV[28].

In our opinion, we should not abandon insulin therapy in neurocritical patients, but a less intensive target should be implemented[11,29,30]. Rigorous studies need to be conducted to ascertain the value of insulin therapy and to define the optimal blood glucose targets in patients with acute cerebrovascular disease.

This survey has certain limitations. First, our findings are only a small and selected sample of what is happening in this part of the world. Therefore, these results should be interpreted carefully as the survey was answered by neurocritical care dedicated physicians from 13 countries, representing <5% of the total number of ICUs in Latin America. Second, although the different questions had been previously tested, it was impossible for us to accurately assess whether they had been interpreted correctly. Third, the replies might not represent real practices. However, we believe this possibility is very low because the survey was completed only by physicians experienced in caring for patients with acute stroke and committed to the aims of LABIC's project.

Fourth, although the response rate was high, we cannot assure that the results are representative of institutions from which we did not receive a response. Nonetheless, this possibility is also unlikely because the characteristics of participating and non-participating institutions were similar, and consequently our sample should not have any inherent bias. Fifth, surveys are useful for defining the state of practice, but they do not provide information on whether the management strategies in its use are correct and properly applied.

Finally, as practice preferences are dynamic, the survey results may change over time, even if the same questions and methodologies are applied.

In conclusion, although most respondents noted the importance of this topic, there was a broad diversity in the definition of HG after an acute stroke. In only half of the respondents, the definition of HG coincides with the threshold used to initiate therapy. Treatment targets also varied substantially among centers. Despite the lack of evidence supporting its application, about one fifth of the respondents still uses IIT. A similar proportion of institutions follow a strict protocol for the management of HG. The heterogeneity observed in different parts of the survey and the current controversy in literature about the optimal control of blood glucose levels in patients with acute stroke, suggest the need of large-scale multicenter studies.

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