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## Original Article

## Factors associated with hypoglycemia in cardiovascular surgery

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## ABSTRACT

**Introduction:** An inadequate glycemic control in cardiovascular postoperative is a predictor of mortality, postoperative infections and a prolonged hospital stay. This study evaluates the incidence of hypoglycemia in the first 72 h of postoperative and its association with different factors, such as tissue perfusion parameters, and the administration of medicines that induct hypoglycemia during surgery, in patients that undergo cardiovascular surgery in a 4th level hospital in Bogota, Colombia.

**Methods and materials:** A nested cases and controls study was developed, taking as cases the patients that presented hypoglycemia episodes (<70 mg/dl) and the controls were the patients without this outcome. A systematic record of the glycemic control in the first 72 h of postoperative was registered. An univariate and multivariate analysis was conducted to determine the factor associated with hypoglycemia.

**Results:** 327 patients were evaluated (35% with coronary bypass and 27% with valvular replacement). 7.65% of the patients presented at least one episode of hypoglycemia <70 mg/dL (25 episodes). The multivariate analysis showed an association with chronic kidney failure in dialysis (OR6,21; IC:0,97–43,27,p:0,05), administration of preoperative steroids (OR4,41; IC:1,27–15,20,p:0,02), intraoperative insulin (OR2,61; IC:1,09–6,22, p:0,03), and postoperative hydrocortisone (OR 7,15; IC 1,46–34,9 p:0,01).

**Conclusions:** Hypoglycemia is frequent in patients that undergo a cardiovascular surgery. The associated factors were chronic kidney failure in dialysis, administration of preoperative steroids, intraoperative insulin and hydrocortisone during postoperative. Other factors such as tissue perfusion, administration of vasoactive or beta blockers substances, showed no association with hypoglycemia.

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## 1. Introduction

The glycemic control in patients that undergo a cardiovascular

surgery is a very important factor to reduce morbimortality in the postoperative of patients with or without diabetes. Multiple studies have demonstrated that an inadequate glycemic control leads patients to an increased risk of infections, a delay in the healing process of the surgical wound, and an increase in acute cardiovascular events [1–3]. A principal objective is the prevention of hypoglycemic and hyperglycemic clinically significant events [4].

It is important to identify the potentially modifiable factors that are associated with hypoglycemia episodes in this type of patients. Previous studies have determine kidney failure with renal replacement therapy, prolonged hospital stay, high variability and

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insulin use, as risk factors of perioperative hypoglycemia, even though there are no new formal evaluations of other potentially modifiable factors associated with hypoglycemia, such as drugs used during surgery or the parameters that suggest postoperative hypoperfusion.

This study evaluates the incidence of hypoglycemia events in the first 72 h of a cardiovascular surgery postoperative, and its association with the patients characteristics, the different types of surgery, the parameters of tissue perfusion like lactic acid and venous oxygen saturation, use of steroids, oral hypoglycemic agents, insulin, vasoactive substances and nutritional agents used before, during and after the procedure.

## 2. Methods and materials

A descriptive observational study of cases and controls was designed, nested in a historical cohort.

All patients who underwent cardiovascular surgery at Hospital Universitario San Ignacio in Bogota, Colombia, during the period between January 2015 and August 2016, were identified. Patients with the following characteristics were selected: patients older than 18 years that underwent myocardial revascularization, valvular replacement, arrhythmia correction surgery, cardiac transplant and/or ascending aortic surgery, which were followed up for at least the first 72 h of postoperative in the intensive care unit. Pregnant women and patients with a concomitant neoplasia were excluded.

The data about patients characteristics, drugs used, perfusion parameters, and glycemic controls taken before, during and after surgical procedure, was collected from the recorded information in

the electronic clinical record, using a preestablished data collection format.

The protocol of glycemic control in patients that are submitted to cardiovascular surgery in the hospital, establishes glycemic targets between 110 and 150 mg/dL. Fig. 1 shows the management algorithm, that includes a capillary glucose measurement every 4 h or more frequently if they are out of target, using a unique equipment (FreeStyle Precision Pro, Abbott, CA). The management is made with crystalline insulin, in continuous infusion, with adjusted doses depending on the capillary glucose measurements.

Hypoglycemia episodes were defined as glucose measurement below 70 mg/dL in the first 72 h of the post operative period. For the analysis the cases where the patients that presented at least one hypoglycemia episode and as controls the ones that didn't present that outcome.

The category variables were presented through frequencies and percentages, meanwhile the continue variables are presented as means and standard deviations, or median and interquartile range, depending on their distribution. The association between hypoglycemia and the clinical factors, the perfusion parameters and use of medications was evaluated initially through an univariate analysis and later they were incorporated in a multivariate logistic regression analysis, including the variables that demonstrated statistically significant association ( $p < 0.05$ ). The data was analyzed with STATA 14.

## 3. Results

The basal characteristics of the 327 included patients are

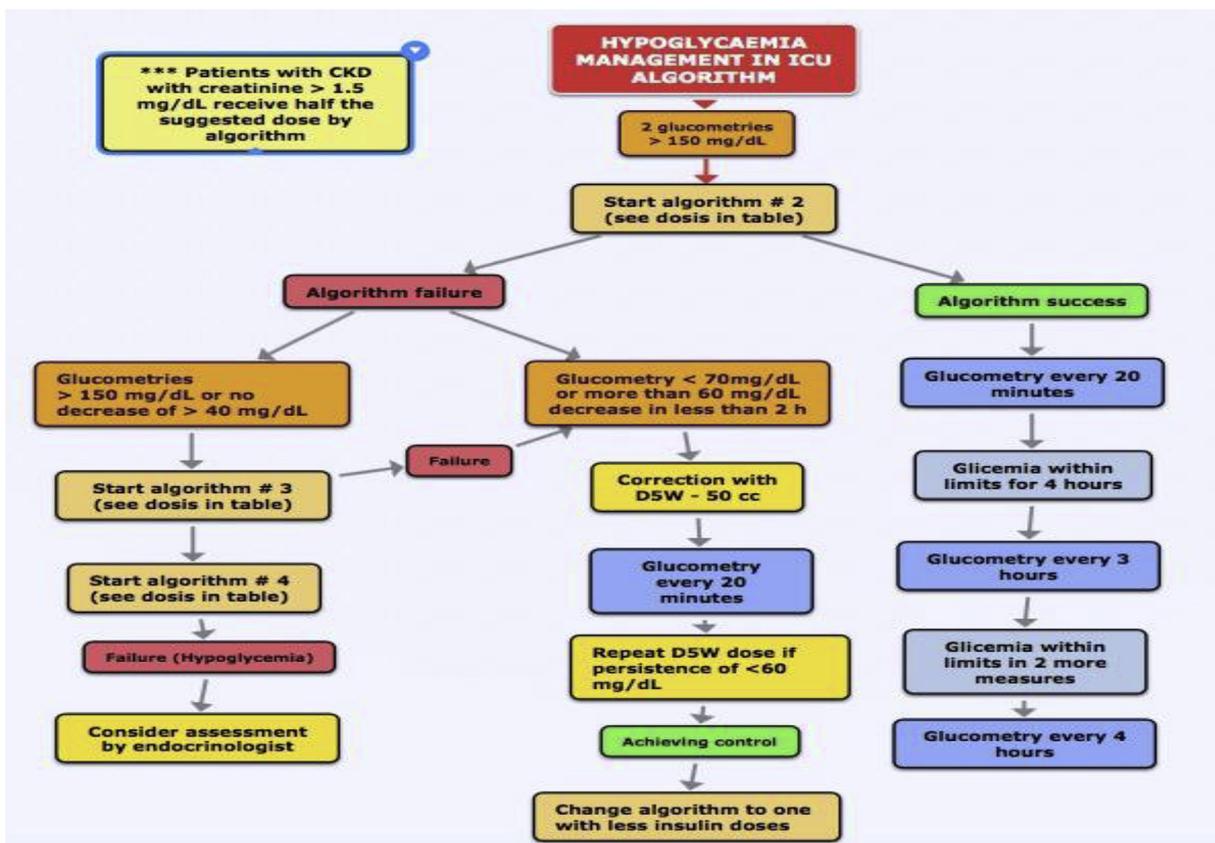


Fig. 1. Algorithm for the management of glycemic control, and in the first 72 h of the postoperative.

Algorithm 1 shows the crystalline insulin doses used at the patients entry to the intensive care unit, administered as a continuous infusion. Patients with chronic kidney disease (defined as creatinine  $> 1.5$  mg/dL) receive half of the doses suggested by the algorithm.

**Table 1**  
Basal patients characteristics.

Variable	n = 327
Masculine sex, n (%)	190 (58,2)
Age in years, media (SD)	60,9 (12,5)
BMI media (SD)	17 (12,6)
Diabetes mellitus, n (%)	
Type 1	2 (0,6)
Type 2	60 (18,3)
Chronic kidney disease, n (%)	37 (11,3)
Renal replacement therapy, n (%)	6 (1,8)
Arterial hypertension, n (%)	200 (61,1)
Dyslipidemia, n (%)	190 (58,1)
Hypothyroidism, n (%)	88 (26,9)
HIV, n (%)	1 (0,3)
Etiology of the baseline heart disease, n (%)	
Coronary	127 (38,8)
Valvular	91 (27,8)
Congenital	11 (3,3)
Mixed	53 (16,2)
Idiopathic	6 (1,8)
Others	39 (11,9)
Preoperative ejection fraction, n (%)	
<40%	49 (14,6)
>40%	278 (84,7)
Alcoholism, n (%)	24 (7,3)
Smoking, n (%)	134 (40,9)

SD: standard deviation, HIV Human immunodeficiency virus.

**Table 2**  
Description of the perioperative management.

Variable	n = 327
Type of surgery, n (%)	
Coronary bypass	116 (35,4)
Valvular replacement	76 (23,2)
Congenital abnormality correction	13 (3,9)
Mixed	66 (20,1)
Biopsy	29 (8,8)
Aortic dissection correction	2 (0,6)
Other	25 (7,4)
Use of preoperative steroids, n (%)	18 (5,5)
Doses > 0.5 mg/kg/day	7 (38,8)
Preoperative use of oral antidiabetics, n (%)	
Biguanides	18 (5,5)
Sulfonylureas	1 (0,3)
DPP4i	4 (1,22)
Multiple oral antidiabetics	20 (6,11)
Preoperative insulin, n (%)	23 (7,03)
Extracorporeal pump, n (%)	
Less than 60 min	20 (6,11)
Equal or greater than 60 min	244 (74,6)
Clamp time, n (%)	
Less than 45 min	53 (16,2)
Between 45 min and 60 min	70 (21,4)
Greater than 60 mi	157 (48,01)
Intraoperative use of steroids, n (%)	73 (22,3)
Intraoperative insulin, n (%)	79 (24,1)
Postoperative use of vasoactive, n (%)	159 (49,09)
Mechanical ventilation, n (%)	169 (51,68)
Tissue perfusion parameters	
POP immediate lactate (mmol/L), median (RIC)	2.2 (1.6–3.3)
24 h POP lactate (mmol/L), media (DE)	1.4 (1.1–2)
Venous saturation < 70%, n (%)	151 (46,6)
Postoperative use of hydrocortisone, n (%)	8 (2,44)

DPP4i: inhibidores de la dipeptidil peptidasa-4, POP: Postoperative, SD (Standard deviation), RIC (Interquartile range).

presented in Table 1. The average age was  $60,9 \pm 12,5$  years and the 58.2% of the patients were men. The most common comorbidities in this group were hypertension (61,1%) and dyslipidemia (58,1%). 62 patients (18,9%) had history of diabetes mellitus, mostly type 2 with an average of HbA1C of 7,2%. 37 patients had history of chronic kidney disease (11,3%). The primary etiology that leads to the cardiovascular surgery was the coronary ischemic disease (38,8%), and in second place the valvular disease (27,8%). The 14,6% of the cases had important compromise of the systolic function with a left ventricular ejection fraction less than 40%.

Table 2 presents the carried out surgical intervention types and the principal characteristics of pre, intra and postoperative management. The most frequent performed procedure was coronary bypass (35,4%), followed by valvular replacement (23,3%). 18 patients received steroids 3 month before the procedure, mostly in doses less than 0,5 mg/kg/day (61,2%). Most of patients with diabetes diagnosis had a previous preoperative management with oral antidiabetics and only 23 of them were receiving insulin, of them the majority had a combination therapy (basal insulin plus a oral antidiabetic).

In the studied population the use of intraoperative steroids was a 22,3% and of insulin was a 24,1%, 5,8% of patients received a dextrose infusion prior to the procedure, in comparison to a 32,1% that required a metabolic flow of dextrose during the postoperative period.

During the surgical postoperative 49% of the patients required vasoactive and/or inotropic support, the median of the lactate values on admission was 2.2 mmol/L (interquartile range 1.6–3.3). At the admission 5.8% presented refractory shock and 1.8% hepatic dysfunction. 8 patients (2,44%) required hydrocortisone and the 34,5% required insulin administration in the first 72 h of the postoperative period, according the glycemic control protocol. Nutrition was initiated in the first 24 h of the postoperative period in the 58,1% of the cases, mostly orally.

34 patients died in the intra and postoperative period (10,3%). The median of the intensive unit care and at halls stay was 4 days (interquartile range of 3–6 days). In total there were documented 25 episodes of hypoglycemia <70 mg/dL (7.5% of the patients included presented at least one episode) and 5 episodes of severe

hypoglycemia.

The association between clinical factors, tissue perfusion parameters and use of perioperative drugs, with the incidence of hypoglycemia in the first 72 h of the postoperative period are showed in Table 3. The univariate analysis demonstrated association between hypoglycemia and chronic kidney disease (OR 2.76; IC 1.02–7.43,  $p=0.04$ ), renal replacement therapy (RRT) (OR 6.43; IC 1.11–37.0,  $p=0.03$ ), preoperative use of steroids (OR 3.90; IC 1.18–12.91,  $p<0.01$ ), requirement of insulin during surgery (OR 2.69; IC 1.16–6.20,  $p=0.02$ ), and use of hydrocortisone in the postoperative (OR 8.10; IC 1.81–36.13,  $p<0.01$ ). The multivariate analysis showed a significant association with chronic kidney disease in renal replacement therapy (OR 6,21; IC:0,97–43,27,  $p=0.05$ ), administration of preoperative steroids (OR4,41; IC:1,27–15,20,  $p=0.02$ ), administration of intraoperative insulin (OR2,61; IC:1,09–6,22,  $p=0.03$ ), and postoperative hydrocortisone (OR 7,15; IC 1,46–34,9  $p=0.01$ ).

#### 4. Discussion

The present work is the first study in Latin America that evaluates the incidence of hypoglycemia episodes in the first 72 h of a cardiovascular surgery postoperative. We demonstrated the association with multiple clinical variables, and includes some additional that have not been studied previously such as tissue perfusion parameters and other potentially modifiable factors like the use of medications before, during and after the procedure.

As starting point the data allowed us to determine the efficacy of a management protocol aimed at maintaining a glycemic control between 110 and 150 mg/dl, like the one that is used in our institution. It draws attention the low incidence of hypoglycemia found

**Table 3**

Association between clinical factors, tissue perfusion parameters and the use of pre, intra and postoperative medications with hypoglycemia.

Variable	Univariate analysis		Multivariate analysis <sup>a</sup>	
	OR (IC)	p	OR (CI)	p
Age in years	0.99 (0.96, 1.03)	0.83		
Diabetes mellitus	1.78 (0.71, 4.48)	0.21		
Chronic kidney disease	2.76 (1.02, 7.43)	0.04		
Renal replacement therapy	6.43 (1.11,37.0)	0.03	6.21 (0.97, 43.27)	0.05
Lactate on admission (mmol/L)	0.95 (0.71, 1.24)	0.78		
Venous saturation <70%	1.52 (0.66, 3.50)	0.32		
Preoperative use of steroids	3.90 (1.18, 12.91)	0.026	4.41 (1.27,15.20)	0.02
Intraoperative use of steroids	2.07(0.87,4.91)	0.09		
POP use of hydrocortisone	8.10(1.81,36.13)	0.006	7.15 (1.46,34.97)	0.01
Preoperative use of oral antidiabetics	2.41(0.90,6.43)	0.08		
Preoperative use of insulin	1.16 (0.25,5.27)	0.84		
Intraoperative use of insulin	2.69(1.16,6.20)	0.02	2.61(1.09,6.22)	0.03
POP use of vasoactives	1.36 (0.60,3.11)	0.45		

<sup>a</sup> Controlling the effect of all statically significant clinical variables, OR: Odds ratio, CI: confidence interval.

(7,65% of the patients included presented at least one episode), compared with other similar studies. The Jonhston study [5] reported that the 21,4% of the population presented one episode of moderate hypoglycemia, this could be related with the fact that in his population there was a higher prevalence of diabetes mellitus and of renal replacement therapy. Likewise, we think these results could be due to the difference between our protocol and the one used in the Johnston study, which is based in the glucommander system [6], that manages standard values in the insulin doses according to the glucometer registry without making adjustments depending on the sensibility of each patient.

Additionally we think that the low prevalence of hypoglycemia evidenced in our population could be a result of a good metabolic control achieved with the institutional management protocol (already described). Added to this, the fact that our institution counts with an individualized nursing staff for each patient that has undergone certain cardiovascular procedures could explain why there is a low incidence, since it assures a narrow control of the individual metabolic parameters and avoids the occurrence of a high number of acute complications, such as hypoglycemia.

Our data emerged from the association of hypoglycemia with certain factors previously described in the literature, such as chronic kidney disease in renal replacement therapy [7], this could be due to the higher insulin blood availability due to a decreased renal excretion. In the same way, the association of the use of intraoperative insulin [7] in this scenario makes its blood concentration to be erratic conditioning hypoglycemia episodes.

It draws the attention the association found in our study with the use of preoperative steroids and the postoperative hydrocortisone. The association between the use of hydrocortisone and hypoglycemia could be influenced by some confusion factors. It is known that some patients receive the hydrocortisone due to a refractory hemodynamic compromise or because of an associated septic shock, being these states a possible reflex of an adrenal axis malfunction that could be related with hypoglycemia. However, it is necessary to perform new clinical studies to evaluate this possible association.

Although it has been described an association between hypoglycemia in patients taken to cardiovascular surgery and the scales that predict mortality [7] such as SOFA and SAPS II, in our study we didn't found that perfusion parameters such as lactic acid, venous saturation, and others, were associated with hypoglycemia.

There are some limitations in the present study; the low incidence of hypoglycemia events reduces the confidence in the evaluation of the magnitude of the effect of the factors found. In the

future, the use of other methods such as the continuous glucose monitoring could improve our capacity to detect hypoglycemia episodes [8]. It is important to highlight the importance to perform new studies that allow us to improve the statistical power, incorporating the new definition of hypoglycemia and severe hypoglycemia.

## 5. Conclusions

It is important to plan the right actions to decrease the hypoglycemia incidence in patients that undergo a cardiovascular surgery aiming to decrease the associated morbimortality. To identify the patients at risk is the first step. Our results showed that the most important associated factors are chronic kidney disease, specially if the patient requires renal replacement therapy, the preoperative pharmacological treatment, specially the use of steroids, and the intraoperative use of insulin.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.dsx.2018.10.009>.

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