[Special article]
Call No. 01/2018 – Publication of scientific articles in the original article and systematic and integrative review categories under the topic "Advanced Nursing Practice: Specialized care and leadership in the building of excellence in nursing".

Original Article

Impact of intensive glycemic control on acute renal injury: a randomized clinical trial

Impacto do controle glicêmico intensivo na lesão renal aguda: ensaio clínico randomizado

Impacto del control glucémico intensivo en la lesión renal aguda: ensayo clínico aleatorizado

Eduesley Santana-Santos[1]
Patrícia Hatanaka Kanke[2,3]
Rita de Cássia Almeida Vieira[3]
Larissa Bertacchini de Oliveira[2,3]
Renata Eloah de Lucena Ferretti-Rebustini[3]
Andreia Freire de Menezes[1]
Íkaro Daniel de Carvalho Barreto[4]
Ludhmila Abrahão Hajjar[2]

Keywords
Hyperglycemia; Cardiac surgical procedures; Acute kidney injury; Insulin

Descritores
Hiperglicemia; Procedimentos cirúrgicos cardíacos; Lesão renal aguda; Insulina

Descriptores
Hiperglucemia; Procedimientos quirúrgicos cardíacos; Lesión renal aguda; Insulina

Submitted
August 29, 2018

Accepted
June 18, 2019

Abstract
Objective: To evaluate the impact of intensive glycemic control on the reduction of the incidence of acute renal injury in adult patients undergoing cardiac surgery.
Methods: Randomized clinical trial, evaluating 95 patients undergoing two glycemic control strategies. Patients were randomized to the intervention n group (IG), with the goal of maintaining postoperative glycemia between 90 and 110 mg/dl. For patients allocated into the conventional group (CG) the goal was to maintain glycaemia between 140 and 180 mg/dl. The insulin dose adjustment was based on undiluted arterial blood glucose measurements at one hour intervals, by means of a blood glucose and beta-ketone monitoring system.
Results: The incidence of acute kidney injury was 53.7% (KDIGO stages 1, 2 or 3). There was no significant difference between the groups regarding the primary outcome (p=0.294). However, a greater frequency of complete renal function recovery (p = 0.010), ICU discharge (p = 0.028), and hospital discharge (p = 0.048) was found among patients undergoing conventional glycemic control. The use of intensive glycemic control was associated with longer ICU stay (p=0.031). The number of episodes of hypoglycemia was similar in both groups (1.6±0.9 vs. 1.3±0.6, p=0.731), demonstrating the safety of the strategies used.
Conclusion: The impact of intensive glycemic control on reducing the incidence of acute kidney injury was not observed. In contrast, patients treated in the CG had a higher frequency of complete renal function recovery.

Resumo
Objetivo: Avaliar o impacto do controle glicêmico intensivo na redução da incidência de lesão renal aguda em pacientes adultos submetidos à cirurgia cardíaca.
Métodos: Ensaio clínico randomizado que avaliou 95 pacientes submetidos a duas estratégias de controle glicêmico. Os pacientes foram randomizados para o grupo intervenção (GI), com a meta de manutenção da glicemia pós-operatória entre 90 e 110 mg/dl. Nos pacientes alocados no grupo convencional (GC) o objetivo era a manutenção da glicemia entre 140 e 180 mg/dl. O ajuste da dose de insulina foi baseado em medições de glicose no sangue arterial não diluído, em intervalos de uma hora por meio de um sistema de monitoramento de glicose e beta-cetona no sangue.
Resultados: A incidência de LRA foi de 53,7% (KDIGO estágios 1, 2 ou 3). Não houve diferença significante entre os grupos quanto ao desfecho primário (p=0,294). Entretanto, observou-se maior frequência de recuperação da função renal (p=0,010), na alta da UTI (p=0,028) e alta hospitalar (p=0,048) entre os pacientes submetidos ao controle glicêmico convencional. A utilização do controle glicêmico intensivo esteve associada com maior tempo de permanência na UTI (p=0,031). O número de episódios de hipoglicemia foi semelhante nos dois grupos (1,6±0,9 vs. 1,3±0,6, p=0,731), demonstrando a segurança das estratégias utilizadas.
Conclusão: Não se observou o impacto do controle glicêmico intensivo na redução da incidência de lesão renal aguda. Em contrapartida, os pacientes tratados no GC apresentaram maior frequência de recuperação da função renal.

Resumen
Objetivo: Evaluar el impacto del control glucémico intensivo en la reducción de la incidencia de lesión renal aguda en pacientes adultos sometidos a cirugía cardíaca.
Métodos: Ensayo clínico aleatorizado que analizó 95 pacientes sometidos a dos estrategias de control glucémico. Los pacientes fueron colocados de forma aleatoria en el grupo experimental (GE), con el objetivo de mantener la glucemia posoperatoria entre 90 y 110 mg/dl. El objetivo para los pacientes ubicados en el grupo convencional (GC) era mantener la glucemia entre 140 y 180 mg/dl. El ajuste de la dosis de insulina se basó en mediciones de glucosa en sangre arterial no diluida, en intervalos de una hora mediante un sistema de monitoreo de glucosa y beta-cetona en sangre.
Resultados: La incidencia de LRA fue de 53,7% (KDIGO nivel 1, 2 o 3). No hubo diferencia significativa entre los grupos con relación al criterio principal de valoración (p=0,294). Sin embargo, se observó mayor frecuencia de recuperación de la función renal (p=0,010), en el alta de la UCI (p=0,028) y alta hospitalaria (p=0,048) en pacientes sometidos al control glucémico convencional. La utilización del control glucémico intensivo estuvo relacionada con mayor tiempo de permanencia en la UCI (p=0,031). El número de episodios de hipoglucemia fue parecido en los dos grupos (1,6 ± 0,9 vs. 1,3 ± 0,6, p=0,731), lo que demuestra la seguridad de las estrategias utilizadas.
Conclusión: No se observó el impacto del control glucémico intensivo en la reducción de la incidencia de lesión renal aguda. Por otro lado, los pacientes tratados en el GC presentaron mayor frecuencia de recuperación de la función renal.

Corresponding author
Eduesley Santana-Santos
https://orcid.org/0000-0001-8545-5677
E-mail: eduesley.santos@gmail.com

DOI
http://dx.doi.org/10.1590/1982-0194201900083

How to cite:
Santana-Santos E, Kanke PH, Vieira RC, Oliveira LB, Ferretti-Rebustini RE, Menezes AF, et al. Impact of intensive glycemic control on acute renal injury: a randomized clinical trial. Acta Paul Enferm. 2019;32(6):592-9.

[1]Universidade Federal de Sergipe, São Cristóvão, SE, Brasil.
[2]Instituto do Coração, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brasil.
[3]Escola de Enfermagem, Universidade de São Paulo, São Paulo, SP, Brasil.
[4]Universidade Federal Rural de Pernambuco, Recife, PE, Brasil.
Conflicts of interest: there are no conflicts of interest to declare.

Introduction

Hyperglycemia, regardless of whether or not diabetes mellitus is present, is one of the main risk factors associated with poor prognosis in patients undergoing cardiac surgery.[1-3] Because it is considered a modifiable risk factor, some studies have highlighted the importance of rigorous glycemic control and its influence on mortality and morbidity, including renal dysfunction.[4,5]

In the current literature, recommendations for glycemic control are mostly derived from studies of critical patients; when assessing renal dysfunction, there is no consensus on standardizing the definition for renal dysfunction.[3,6] A limited number of studies[1,7] focused on the use of an intensive glycemic control protocol to reduce the incidence of acute kidney injury (AKI); no study specifically investigated the outcome of intensive treatment in renal function using the most current international classification of AKI, Kidney Disease: Improving Global Outcomes (KDIGO).[8] Consequently, the comparison of findings from different studies is compromised due to the heterogeneity of these results.

Acute kidney injury, defined based on elevated serum creatinine levels, occurs in almost 25% of patients in the first days after cardiac surgery, speculatively as a result of postoperative hypotension, use of nephrotoxic substances, and inflammation.[9,10] Acute kidney injury is a frequent complication after cardiac surgery, with an incidence ranging from 20% to 57%.[11,12] When it occurs in the cardiac surgery postoperative period, it is associated with an increase in hospitalization costs, longer hospital stays, increased time on mechanical ventilation, increased rates of wound infection and mortality, especially when there is a need for dialysis.[13-16] Although the exact mechanisms responsible for postoperative AKI remain uncertain, its prognostic impact is well documented, not only in terms of morbidity but also in long-term events, such as incomplete recovery of renal function, and progression to chronic kidney disease, cardiovascular events, and death.[15,17]

Hyperglycemia has been suggested as a risk factor for the development of postoperative AKI.[1,3,7] However, the method for obtaining the best hyperglycemic control in the cardiac surgery setting remains uncertain. Thus, the objective of this study was to evaluate the impact of intensive glycemic control in reducing the incidence of acute renal injury in adult patients undergoing cardiac surgery, when compared to conventional glycemic control.

Methods

This was a randomized controlled trial, performed in a teaching hospital that is a reference site in Cardiology, Cardiac and Thoracic Surgery, located in the state of São Paulo, Brazil. The methodology of the study was based upon the recommendations of the Consort Statement. The study was enrolled in ClinicalTrials.gov, under the identifier NCT02574156, and acronym CHYCS - Control of Hyperglycemia After Cardiac Surgery: CHyCS Trial.

Patients undergoing cardiac surgery from May of 2016 to December of 2016, who presented glycemia greater than or equal to 200 mg/dl in the first six hours of admission to the surgical ICU (SICU) were included. Patients younger than 18 years of age, hospitalized for surgical correction of congenital heart disease, cardiac transplant, and/or participating in another study were excluded, as well as patients with a diagnosis of chronic renal failure undergoing on dialysis. The researchers selected patients who were candidates for inclusion in the study on the day before the surgical procedure, by analyzing the surgical schedule established for the subsequent date. The candidates were carefully informed by the researchers regarding the objectives of the study, and if they agreed to participate, they were included in the study protocol.

All patients received standard surgical care as previously described.[12] In summary, patients received general anesthesia that was induced using fentanyl, midazolam, etomidate and pancuronium, adjusted for weight, and maintained with fentanyl and inhaled isoflurane. The decision to use extracorporeal circulation (EC) was the decision of the surgeon, and all surgical procedures were performed

by median sternotomy. After surgery, all patients were transferred to the SICU.

Patients who had glycemia above 200 mg/dl in the first six hours of admission to the SICU were randomized, using a random list generated through a computer program (www.random.org), and were allocated to one of the groups: the conventional group (CG) with the objective of maintaining glycemia between 140 mg/dl and 180 mg/dl, or the intensive group (IG), with the aim to maintain glycemia between 90 mg/dl and 110 mg/dl. The conventional glycemic control target is used routinely in the SICU where the study was conducted.

The patients included were monitored for capillary glycemia at one hour intervals during the first 24 hours postoperatively, and received glucose solution during their time on the protocol (400 ml of 10% glucose solution, and 100 ml of 50% glucose) and an infusion of insulin in the dilution of 100 IU of regular insulin and 100 ml of saline solution (0.9% NaCl) in a continuous infusion pump. The insulin dose adjustment was based on undiluted arterial blood glucose measurements, taken at one-hour intervals, using a blood glucose and beta-ketone monitoring system (Freestyle Precision Pro, Abbott®). The insulin dose was adjusted based on an algorithm[4] adapted for this study by a team of intensive care nurses trained for this purpose, and assisted daily by a research nurse not involved in the clinical care of the patients.

For the sample calculation, we defined 5% alpha (α), with 80% power, to reduce the absolute incidence of acute renal injury from 57% to 28.5%, totaling 94 patients. After ascertaining the eligibility of the participants, the randomization was by aleatory method, in blocks of ten, from a list of random numbers generated by the website: www.randomization.org.

For data collection, a specific instrument was developed with information on patient identification, demographics, clinical characteristics, procedural data, clinical evaluation, and outcomes.

Surgical risk assessment was assessd using the European system for cardiac operative risk evaluation (EuroSCORE), assessment of the degree of organ dysfunction in the ICU using the Sequential Organ Failure Assessment Score (SOFA Score), the prognosis evaluation via the Simplified Acute Physiology Score III (SAPS 3), prediction of AKI in the cardiac surgery postoperative period using the Cleveland Clinic Scoring Tool, and the evaluation of comorbidities and prediction of mortality in ten years using the Charlson Comorbidity Index.

The primary outcome was the reduction in the incidence of AKI in the postoperative cardiac surgery period. For the definition of AKI, the KDIGO criterion[8] was used, which defines AKI as an absolute increase in creatinine levels of at least 0.3 mg/dl in the last 48 hours, or a relative increase in creatinine of at least 1.5 times from baseline in the last seven days, or a urine output <0.5 ml/kg/hour in the last six hours. Only one of these criteria (increase in creatinine or reduction of urine output) is necessary for establishment of AKI. This classification stratifies the AKI in three stages, as noted in chart 1. The secondary outcomes evaluated were the need for dialysis, recovery of renal function, discharge from SICU and from the hospital, death, hypoglycemia (capillary glycemia <70mg/dL), number of episodes of hypoglycemia, and the length of stay in SICU and in the hospital.

Chart 1. Classification of acute kidney injury according to the KDIGO criterion

Stage	Serum creatinine	Urinary output
1	Increase in Cr > to 0.3 mg/dl (≥ 26.4 µmol/l) or increase of 1.5 - 1.9 times baseline Cr	< 0.5 ml/kg/hr for 6-12h
2	Increase in Cr > 2 - 2.9 times baseline Cr	< 0.5 ml/kg/h for > 12h
3	Increased Cr >3 times baseline Cr, or Cr > to 4.0 mg/dl [≥ 354 µmol/l], OR beginning of renal replacement therapy, OR GFR decreased to <35 ml/min in patients < 18 years of age.	< 0.3 ml/kg/h for > 24h, or anuria for > 12h

Source: translated from Khwaja KDIGO clinical practice. guidelines for acute kidney injury. Nephron Clin Pract. 2012; 120 (4): e179-84.
[S]Cr – Serum creatinine; GFR - Glomerular filtration rate

The data were described by means of absolute frequencies and relative percentages when categorical, and using means and standard deviations when continuous. The associations between categorical variables and treatment types were tested by Pearson's Chi-Square test, estimated via the Monte Carlo procedure (100,000 replications). Differences in measures of central tendency among types of treatments were tested using the Mann-Whitney test. To evaluate the associations between three or

more categorical variables, a perceptual map estimated by Multiple Correspondence Analysis was used. The significance level adopted was 5%, and the software used was the R Core Team, 2018.

The study was submitted and registered in the Brazil Platform under the Certificate of Presentation for Ethical Appreciation (CAEE) 50949115.5.0000.0068, and approved by the Research Ethics Committee of the Faculty of Medicine of the University of São Paulo, under the number 1,378,648. All participants signed the Terms of Free and Informed Consent. The study complied with national and international standards of research ethics involving human subjects, in accordance with resolution 466/12.

Results

During the data collection period, 95 patients were selected for the study, among 440 eligible patients (Figure 1). The comparative analysis between the clinical and demographic characteristics of the individuals studied shows that the IG and CG groups were homogeneous, except for the use of vasoactive substances, which was higher in the IG group. The participants were mostly males (54.7%), mean age 59.8 ± 12.8 years, at low risk for death and development of AKI, as demonstrated by the Euroscore (3.4 ± 2.6) and the Cleveland Clinic Scoring Tool (2.2 ± 1.5), respectively. The severity profiles, measured by SAPS 3 scores on admission to the SICU (p=0.681), and the SOFA after 24 hours (p=0.544), were also similar between groups. The most frequent type of surgery was myocardial revascularization surgery using the saphenous vein (37.9%) and mammary artery (36.8%). It was necessary to use EC in 96.8% of patients, with a mean time of 91.7 ± 33.2 minutes. The treatment with vasoactive substances was different between groups (97.2% vs. 83.1%, p=0.047) in IG and CG, respectively, even though severity assessed by SAPS 3 was similar between the groups (p=0.681). However, there was no difference in the doses of dobutamine (p=0.518) or noradrenaline (p=0.218) between groups. The clinical and demographic characteristics of patients undergoing glycemic control in both groups are presented in table 1.

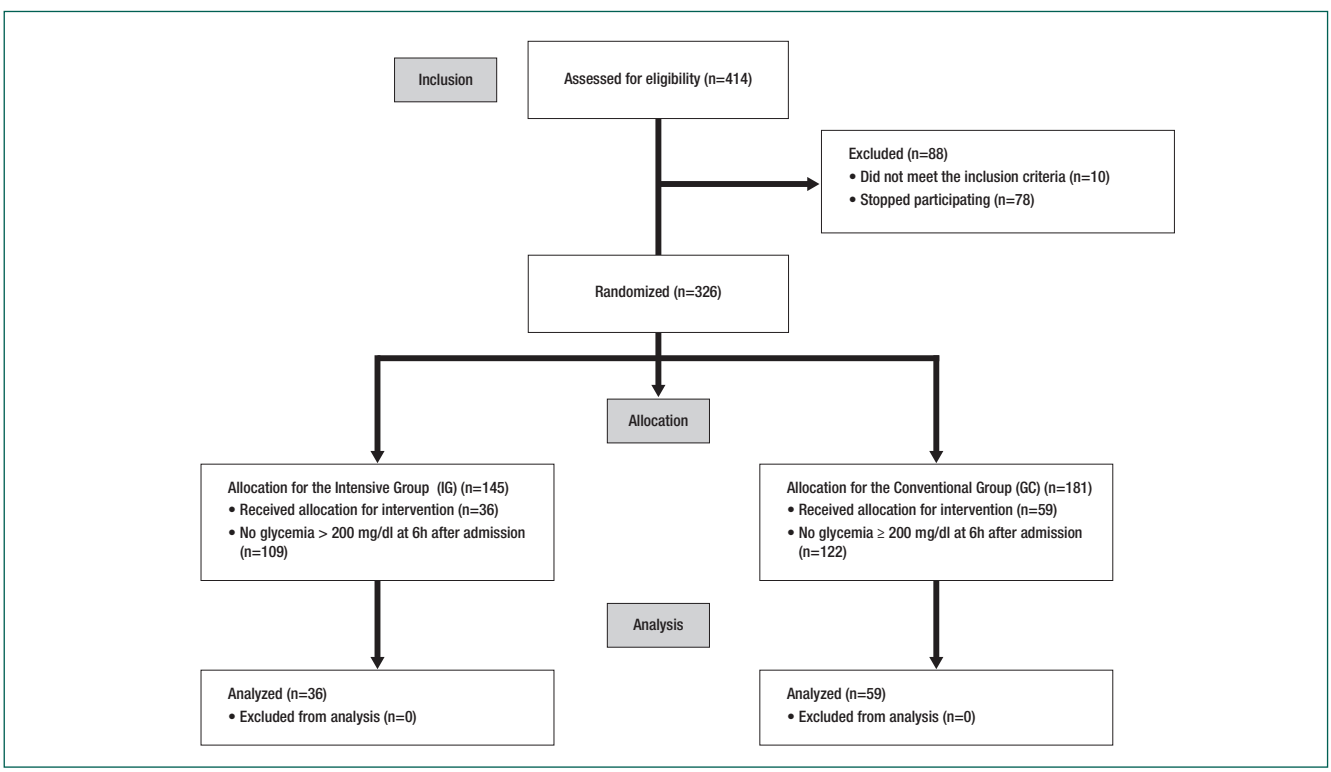

Figure 1. Flowchart for inclusion, allocation, and analysis of the research sample based on recommendations of the CONSORT Statement

Table 1. Clinical and demographic characteristics of patients undergoing glycemic control in the Intensive Group (IG) and the Conventional Group (CG)

Variables	Total (n=95) n(%)	IC (n=36) n(%)	CG (n=59) n(%)	*p-value*
Sex, n (%)				
Male	52(54.7)	19(52.8)	33(55.9)	0.833*
Female	43(45.3)	17(47.2)	26(44.1)	
Age, years (mean + SD)	59.8(12.8)	60(12.5)	59.7(13.2)	0.997#
EuroSCORE, (mean + SD)	3.4(2.6)	3.7(3.1)	3.3(2.2)	0.888#
Cleveland Clinic Scoring Tool, (mean + SD)	2.2(1.5)	2.2(1.7)	2.2(1.3)	0.413#
Charlson Comorbidity Index, (mean + SD)	2.7(1.8)	2.7(1.8)	2.8(1.9)	0.779#
LVEF, (mean + SD)	55.3(16.5)	54(17.9)	56.1(15.7)	0.764#
Baseline creatinine, mg/dL (mean + SD P)	1.2(0.7)	1.1(0.6)	1.2(0.8)	0.288#
GFR, mL/min (mean + SD)	54.1(10.9)	55.9(9.9)	53(11.4)	0.118#
Baseline glycemia, (mean + SD)	135.3(64)	128.4(46.6)	139.3(72.3)	0.948#
Inclusion gycemia, (mean + SD)	235.7(37.9)	236.8(44.6)	235(33.6)	0.654#
Comorbities, n (%)				
Previous AMI	20(21.1)	11(30.6)	9(15.3)	0.118*
Systemic arterial hypertension	63(66.3)	23(63.9)	40(67.8)	0.823*
Dyslipidemia	35(36.8)	12(33.3)	23(39)	0.664*
Active smoker	9(9.5)	3(8.3)	6(10.2)	1.000*
Chronic kidney disease	14(14.7)	4(11.1)	10(16.9)	0.557*
Atrial fibrillation	19(20)	8(22.2)	11(18.6)	0.793*
Diabetes	40(42.1)	13(36.1)	27(45.8)	0.397*
Previous cerebrovascular attack	6(6.3)	2(5.6)	4(6.8)	1.000*
Previous cardiac surgery, n (%)	12(12.6)	5(13.9)	7(11.9)	0.761*
Type of surgery, n (%)				
MRI – Mammary	35(36.8)	13(36.1)	22(37.3)	1.000*
MRI – Saphenous	36(37.9)	13(36.1)	23(39)	0.830*
Valve – Mitral	26(27.4)	13(36.1)	13(22)	0.159*
Valve – Aortic	34(35.8)	11(30.6)	23(39)	0.509*
Aortic surgery	3(3.2)	3(8.3)	0(0)	0.052*
EC, n (%)	92(96.8)	34(94.4)	58(98.3)	0.555*
Time in EC, (mean + SD)	91.7(33.2)	89.5(37.7)	93(30.4)	0.809#
Time anoxic, (mean + SD)	68(26.5)	63.2(27.7)	70.9(25.5)	0.365#
Time in surgery, (mean + SD)	505.6(107.4)	519.1(127.8)	497.4(93.1)	0.629#
Transfusion of blood derivatives, n (%)	26(27.4)	12(33.3)	14(23.7)	0.348#
Use of VAs, n (%)	84(88.4)	35(97.2)	49(83.1)	0.047*
Dose of vasoactive agents				
Dobutamine, mcg/kg/min (mean + SD)	6.8(5.8)	7.1(5.6)	6.6(5.9)	0.518#
Norepinephrine, mcg/kg/min (mean + SD)	0.1(0.1)	0.1(0.1)	0.1(0.2)	0.218#
Diuresis, ml/kg/h (mean + SD)	2.6(1.4)	2.7(1.1)	2.6(1.5)	0.432#
Intraoperative HB, (mean + SD)	80.4(410.5)	37.5(15.6)	106.6(520.7)	0.610#
SAPS III at admission, (mean + SD)	33.5(5.8)	33.9(5.7)	33.3(6)	0.681#
SAPS III at discharge, (mean + SD)	9.6(6.5)	9.7(7.9)	9.6(5.7)	0.595#
SOFA after 24h of admission, (mean + SD)	11.8(1.2)	11.7(1.1)	11.8(1.3)	0.544#
SOFA at discharge, (mean + SD)	1.8(1.3)	1.7(1.4)	1.8(1.3)	0.680#

n - absolute frequency; % - relative frequency; SD - standard deviation; LVEF - left ventricular ejection fraction; GFR - glomerular filtration rate; AMI - acute myocardial infarction; MRI - myocardial revascularization; EC- extracorporeal circulation; VA - vasoactive agent; HB- hydric balance; SAPS - simplified acute physiology score; SOFA - sequential organ failure assessment; * Pearson's Chi-Square test; # Mann-Whitney test.

Table 2 presents the outcomes of patients undergoing glycemic control in the intensive and conventional groups. The incidence of AKI was 53.7% (KDIGO stages 1, 2 or 3). The AKI analyzed in the three stages, separately, demonstrated that among the 51 patients with AKI, 41 were classified as stage 1, seven as stage 2, and only three as stage 3. These results reflect the low severity of AKI associated with the surgical procedure in this sample. There was a higher frequency of renal function recovery (69.5% vs. 41.7%, p=0.010), and more rapid discharge from the SICU (98.3% vs. 86.1%, p=0.028) and the hospital (96.6% vs. 82.4%, p=0.048) among the CG patients when compared to the IC patients. Those patients undergoing intensive glycemic control had a longer stay in the SICU when compared to those treated with conventional control (p = 0.031).

Table 2. Outcomes presented by patients undergoing glycemic control in the Intensive Group (IG) and the Conventional Group (CG)

Outcome	Total (n=95) n(%)	IC (n=36) n(%)	CG (n=59) n(%)	p-value
Primary				
AKI, n (%)	51(53.7)	22(61.1)	29(49.2)	0.294*
KDIGO Stage 1, n (%)	41(43.2)	17(47.2)	24(40.7)	0.670*
KDIGO Stage 2, n (%)	7(7.4)	3(8.3)	4(6.8)	1.000*
KDIGO Stage 3, n (%)	3(3.2)	2(5.6)	1(1.7)	0.555*
Secondary				
Death, n (%)	5(5.3)	4(11.1)	1(1.7)	0.066*
Dialysis, n (%)	5(5.3)	3(8.3)	2(3.4)	0.364*
Recovery of renal function, n (%)	56(58.9)	15(41.7)	41(69.5)	0.010*
Hypoglycemia, n (%)	8(8.4)	5(13.9)	3(5.1)	0.151*
ICU discharge, n (%)	89(93.7)	31(86.1)	58(98.3)	0.028*
Hypoglycemia episodes, (mean + SD)	1.5(0.8)	1.6(0.9)	1.3(0.6)	0.731#
LOS-SICU, days (mean + SD)	4.7(3.5)	5.7(4.2)	4.2(3)	0.031#
LOS-Hospital, days (mean + SD)	11.7(8.8)	11.2(8.9)	12(8.8)	0.839#

n - absolute frequency; % - relative frequency; SD - standard deviation; AKI - acute kidney injury; ICU - intensive care unit; LOS-SICU - length of stay-surgical intensive care unit; LOS-Hospital - length of stay-Hospital; * Pearson's Chi-Square test; # Mann-Whitney test.

Discussion

The main findings of this study demonstrate that the use of intensive glycemic control did not reduce the incidence of AKI when compared to conventional glycemic control in adult patients undergoing cardiac surgery, and that its use was associated with worse outcomes. Hyperglycemia is a common problem in the postoperative cardiac surgery peri-

od, and an important risk factor for the development of complications, including the risk of surgical wound infection, stroke, sepsis, need for prolonged mechanical ventilation, longer length of stay, and death.[6,18,20] It is known that a complex interaction between endogenous catecholamines, cytokines and the activation of the hypothalamic-pituitary-adrenal axis is involved in the pathogenesis of "stress hyperglycemia", which results in excessive induction and secretion of cortisol and gluconeogenesis. Supposed pathophysiological mechanisms by which hyperglycemia can aggravate the outcomes include the promotion of oxidative stress pathways and the induction of inflammation. [21,22]

Because hyperglycemia is a potentially modifiable risk factor, it is fundamental to establish a protocol that implies greater postoperative control. Van den Berghe et al. [23] were the first researchers to investigate the effects of intensive GC in patients from SICU, and their findings showed a reduction in mortality and renal dysfunction in this group of patients in which the glycemic goal was 80 - 110 mg/dL. Later, the same group of investigators evaluated the effect of the same intensive treatment protocol on patients in a clinical ICU, and likewise found a reduction in the incidence of renal dysfunction in that population.[5] In a more detailed evaluation of renal function in these two studies, the incidence of renal dysfunction was lower in patients who maintained a blood glucose < 110 mg/dL, and higher in those with a blood glucose level > 150 mg/dL. In contrast, the intensive GC did not show a positive impact on the reduction of acute renal injury in our study. While Van den Berghe considered renal dysfunction to be an increase in baseline creatinine of > 2.5 mg / dL ,or as the need for dialysis, we used the most current definition for AKI, the KDIGO classification, that is a more sensitive tool for assessment of renal injury which enables earlier diagnosis, and supports a better comparison of the results from different studies.

Subsequent studies to reaffirm the effect of intensive GC showed contradictory results. Two randomized controlled trials, which examined the effect of intensive treatment (with a glycemic target between 80 - 110 mg/dL) compared to a conventional protocol where the target was between 140 - 180 mg/dL in intensive care units, were interrupted early due to safety issues related to the increased incidence of severe hypoglycemia in patients allocated to the intensive treatment group.[24,25] Contrary to what was observed in these studies, our study showed a similar number of episodes of hypoglycemia in the two groups: 1.6 + 0.9 vs. 1.3 + 0.6, p=0.731, respectively, in IG and CG patients. This demonstrates that, even with no impact on the primary outcome, the protocol used and hourly monitoring of the blood glucose by the team of nurses involved in the research, corroborated to this aspect of safety.

Another interesting finding of this study was that patients in the IG had lower SICU discharge frequency (p=0.028) and longer SICU stay (p=0.031), when compared with the CG. However, no difference was observed between groups in relation to mortality. These findings are in contrast to those published in the meta-analysis by Haga and colleagues [26], which identified that intensive GC was associated with a reduction in mortality up to 30 days after surgery, incidence of atrial fibrillation, need for mechanical ventilation, and ICU stay after cardiac surgery. However, this review has important limitations, among them: the reduced number of randomized clinical trials included; small number of patients included in each of the studies evaluated; and important methodological differences between the studies regarding the definitions used for intensive GC.

In a recent study, Giakoumidakis and his colleagues[27] randomized 212 patients into two GC protocols (one intensive and one control). The results showed that patients treated with the intensive protocol had lower mortality rates (p=0.033). However, the glycemic target defined by these researchers as intensive was similar to that established in our study for the conventional group (120 - 160 mg/dL). In addition, the data published by Giakoumidakis et al. contrast with those of the classic NICE-SUGAR study [28], which showed an association of intensive control with mortality in a multicenter clinical trial involving 6104 patients.

Several studies [29-32] have already demonstrated the association between hyperglycemia and acute

renal injury, although most of them use different definitions for AKI, ranging from small increases in serum creatinine to the need for dialysis. In our study, despite the high incidence of AKI in both groups, there was no significant difference between the groups, and the recovery of complete renal function was higher among those in the conventional group (p=0.010). A possible explanation for this fact is that the use of higher doses of insulin to maintain a target of lower glycemia, as happened in the IG, implies a greater variation of glycemia and consequently an increase of oxidative stress. Other studies have already demonstrated the relationship between oxidative stress and a higher incidence of AKI [12,33] , as well as delayed recovery of complete renal function and longer hospital stay .[30]

This study has implications for nursing practice, as the implementation of the protocol and the conduct of the research was done exclusively by specialist nurses, masters' and doctorally prepared, with extensive experience in the area of cardiology. This high degree of qualification of the professionals, and their involvement in the application of evidence-based practices, implies a higher quality of care provided to the patients, configured as advanced nursing practice.

This study has limitations. First, it is a single-center study and the number of patients was relatively small. More importantly, although hardly predictable, the number of serious renal events was less than expected. Second, it was not possible to conduct the study with a strict blindness of the researchers; because the dose of insulin required adjustment to achieve the target of each group, monitoring of blood glucose was necessary. Finally, this study involved only patients undergoing cardiac surgery, and for this reason it is not possible to extrapolate the results obtained for patients undergoing other types of surgical procedures, or even patients admitted to the general ICU.

Conclusion

Notwithstanding the safety of both protocols for GC used in this study, the impact of intensive GC on reducing the incidence of acute renal injury was not noted. The results indicate a relationship between conventional GC with higher frequencies of renal function recovery, episodes of hypoglycemia, and discharge from the ICU.

Collaborations

Kanke PH, Veira RCO, Ferretti-Rebustini REL, Oliveira LB e Menezes AF contributed to the data interpretation, article writing, critical analysis of the relevant content, and final approval of the version to be published. Barreto IDC contributed to the study analysis and data interpretation. Santana-Santos E e Hajjar LA contributed to the study design, analysis, data interpretation, article writing, critical analysis of the relevant content, and final approval of the version to be published.

References

1. Song JW, Shim JK, Yoo KJ, Oh SY, Kwak YL. Impact of intraoperative hyperglycaemia on renal dysfunction after off-pump coronary artery bypass. Interact Cardiovasc Thorac Surg. 2013;17(3):473–8.
2. Umpierrez G, Cardona S, Pasquel F, Jacobs S, Peng L, Unigwe M, et al. Randomized controlled trial of intensive versus conservative glucose control in patients undergoing coronary artery bypass graft surgery: GLUCO-CABG Trial. Diabetes Care. 2015;38(9):1665–72.
3. Fiaccadori E, Sabatino A, Morabito S, Bozzoli L, Donadio C, Maggiore U, et al. Hyper/hypoglycemia and acute kidney injury in critically ill patients. Clin Nutr. 2016;35(2):317–21.
4. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359–67.
5. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354(5):449–61.
6. Arnold SV, Lipska KJ, Wang J, Seman L, Mehta SN, Kosiborod M. Use of intensive glycemic management in older adults with diabetes mellitus. J Am Geriatr Soc. 2018;66(6):1190–4.
7. Giannini F, Latib A, Jabbour RJ, Ruparelia N, Aurelio A, Ancona MB, et al. Impact of post-procedural hyperglycemia on acute kidney injury after transcatheter aortic valve implantation. Int J Cardiol. 2016;221:892–7.
8. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120(4):e179–84.
9. Kidher E, Harling L, Ashrafian H, Naase H, Chukwuemeka A, Anderson J, et al. Pulse wave velocity and neutrophil gelatinase-associated lipocalin as predictors of acute kidney injury following aortic valve replacement. J Cardiothorac Surg. 2014;9(1):89.

10. Wang Y, Bellomo R. Cardiac surgery-associated acute kidney injury: risk factors, pathophysiology and treatment. Nat Rev Nephrol. 2017;13(11):697–711.

11. Ninni S, Seunes C, Ortmans S, Mouton S, Modine T, Koussa M, et al. Peri-operative acute kidney injury upon cardiac surgery time-of-day. Int J Cardiol. 2018;272:54–9.

12. Santana-Santos E, Gowdak LH, Gaiotto FA, Puig LB, Hajjar LA, Zeferino SP, et al. High dose of N-acetylcystein prevents acute kidney injury in chronic kidney disease patients undergoing myocardial revascularization. Ann Thorac Surg. 2014;97(5):1617–23.

13. Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT; The Multicenter Study of Perioperative Ischemia Research Group. Renal dysfunction after myocardial revascularization: risk factors, adverse outcomes, and hospital resource utilization. Ann Intern Med. 1998;128(3):194–203.

14. Lo LJ, Go AS, Chertow GM, McCulloch CE, Fan D, Ordoñez JD, et al. Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. Kidney Int. 2009;76(8):893–9.

15. Hobson C, Ozrazgat-Baslanti T, Kuxhausen A, Thottakkara P, Efron PA, Moore FA, et al. Cost and mortality associated with postoperative acute kidney injury. Ann Surg. 2015;261(6):1207–14.

16. Najjar M, Yerebakan H, Sorabella RA, Donovan DJ, Kossar AP, Sreekanth S, et al. Acute kidney injury following surgical aortic valve replacement. J Card Surg. 2015;30(8):631–9.

17. Santana-Santos E, Kamei FK, do Nascimento TK, Abou Ismail A, Herbas Palomo JS, da Silva Magro MC, et al. Long-term follow-up evaluation of renal function in patients with chronic kidney disease undergoing cardiac surgery. Int J Nephrol. 2016;2016:9680718.

18. Trence DL, Kelly JL, Hirsch IB. The rationale and management of hyperglycemia for in-patients with cardiovascular disease: time for change. J Clin Endocrinol Metab. 2003;88(6):2430–7.

19. Warren B, Rebholz CM, Sang Y, Lee AK, Coresh J, Selvin E, et al. Diabetes and trajectories of estimated glomerular filtration rate: a prospective cohort analysis of the atherosclerosis risk in communities study. Diabetes Care. 2018;41(8):1646–53.

20. Buehler L, Fayfman M, Alexopoulos AS, Zhao L, Farrokhi F, Weaver J, et al. The impact of hyperglycemia and obesity on hospitalization costs and clinical outcome in general surgery patients. J Diabetes Complications. 2015;29(8):1177–82.

21. Abdelmalak BB, Knittel J, Abdelmalak JB, Dalton JE, Christiansen E, Foss J, et al. Preoperative blood glucose concentrations and postoperative outcomes after elective non-cardiac surgery: an observational study. Br J Anaesth. 2014;112(1):79–88.

22. Umpierrez GE, Kosiborod M. Inpatient dysglycemia and clinical outcomes: association or causation? J Diabetes Complications. 2014;28(4):427–9.

23. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet. 2009;373(9677):1798–807.

24. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, et al.; German Competence Network Sepsis (SepNet). Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008;358(2):125–39.

25. Preiser JC, Devos P, Ruiz-Santana S, Mélot C, Annane D, Groeneveld J, et al. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. Intensive Care Med. 2009;35(10):1738–48.

26. Haga KK, McClymont KL, Clarke S, Grounds RS, Ng KY, Glyde DW, et al. The effect of tight glycaemic control, during and after cardiac surgery, on patient mortality and morbidity: A systematic review and meta-analysis. J Cardiothorac Surg. 2011;6(1):3.

27. Giakoumidakis K, Eltheni R, Patelarou E, Theologou S, Patris V, Michopanou N, et al. Effects of intensive glycemic control on outcomes of cardiac surgery. Heart Lung. 2013;42(2):146–51.

28. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, et al.; NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283–97.

29. Chiu PF, Wu CL, Huang CH, Liou HH, Chang CB, Chang HR, et al. Lower blood glucose and variability are associated with earlier recovery from renal injury caused by episodic urinary tract infection in advanced type 2 diabetic chronic kidney disease. PLoS One. 2014;9(9):e108531.

30. Moriyama N, Ishihara M, Noguchi T, Nakanishi M, Arakawa T, Asaumi Y, et al. Admission hyperglycemia is an independent predictor of acute kidney injury in patients with acute myocardial infarction. Circ J. 2014;78(6):1475–80.

31. Gordillo R, Ahluwalia T, Woroniecki R. Hyperglycemia and acute kidney injury in critically ill children. Int J Nephrol Renovasc Dis. 2016;9:201–4.

32. Azevedo JR, Azevedo RP, Lucena LC, Costa NN, Silva WS. Impact of glycemic control on the incidence of acute kidney injury in critically ill patients: a comparison of two strategies using the RIFLE criteria. Clinics (São Paulo). 2010;65(8):769–73.

33. Yoo S, Lee HJ, Lee H, Ryu HG. Association between perioperative hyperglycemia or glucose variability and postoperative acute kidney injury after liver transplantation: A retrospective observational study. Anesth Analg. 2017;124(1):35–41.