Preoperative glutamine infusion improves glycemia in heart surgery patients[1]

Infusão pré-operatória de glutamina melhora a glicemia em pacientes submetidos à cirurgia cardíaca

Miguel Nasser Hissa[I], Raquel Cavalcante de Vasconcelos[II], Sergio Botelho Guimarães[III], Ricardo Pereira Silva[IV], José Huygens Parente Garcia[V], Paulo Roberto Leitão de Vasconcelos[VI]

[I]Fellow PhD Degree, Department of Surgery, Postgraduate Program, UFC, Ceara, Brazil. Technical procedures, acquisition and interpretation of data. The article is part of a doctorate thesis level.
[II]Graduate student, UFC, Ceara, Brazil. Helped with technical procedures, acquisition of data.
[III]PhD, Associate Professor, Department of Surgery, Head, LABCEX, UFC, Ceara, Brazil. Manuscript writing, statistical analysis, graphics design.
[IV]PhD, Associate Professor, Head, Department of Surgery, UFC, Ceara, Brazil. Critical revision and analysis of data.
[V]PhD, Associate Professor, Department of Clinical Medicine, UFC, Ceara, Brazil. Critical revision and analysis of data.
[VI]Ph.D, Associate Professor, Coordinator, Postgraduate Program, Department of Surgery, UFC, Ceara, Brazil. Tutor, responsible for conception, design, intellectual and scientific content of the study, critical analysis, final approval of manuscript.

ABSTRACT
PURPOSE: To evaluate the effects of pre-operative L-alanyl-glutamine (L-Ala-Gln) on blood glucose control in patients with coronary obstruction, selected for myocardial revascularization.
METHODS: Twenty-two patients (63±8 years) were randomly assigned to receive 250ml of L-Ala-Gln 20% plus saline 750 ml (Group L- Ala-Gln, n=11) or saline 1000 ml (Group Saline, n=11) over 3 hours before operation. Pre-operative blood samples were collected 3h before (T-1) and at the beginning of the surgical procedure (T-2). Intra-operative samples were collected immediately before the start (T-3) and the end of extra-corporeal perfusion (T- 4). Post-operative samples were collected 12h (T-12) and 24h later (T-24).
RESULTS: Glycemia decreased significantly in L-Ala-Gln treated patients during the intraoperative period. The same effect did not occur in saline patients. As the rate of insulin infusion, administered routinely to patients undergoing surgery with extracorporeal circulation was constant in both groups during surgery, the reduction of blood glucose in group L-Ala-Gln does not seem to be related to exogenous insulin.
CONCLUSION: Pre-operative use of L-Ala-Gln improves glycemic control in patients with coronary artery occlusion, submitted to myocardial revascularization.
Keywords: Glutamine. Blood Glucose. Metabolism. Coronary Artery Disease. Cardiovascular Surgical Procedures.

RESUMO
OBJETIVO: Avaliar os efeitos do uso pré-operatório da L-alanil-glutamina (L-Ala-Gln) no controle glicêmico em pacientes, selecionados para a revascularização do miocárdio.
MÉTODOS: Vinte e dois pacientes cardiopatas (63±8 anos) foram randomizados para receber 250 ml de L-Ala-Gln 20% em 750 ml de solução salina (Grupo L-Ala-Gln, n=11) ou soro fisiológico 1000 ml (Grupo Salina, n=11). Amostras de sangue foram coletadas no pré-operatório, três horas antes (T-1: basal) e no início do procedimento cirúrgico (T-2); imediatamente antes do início (T-3) e no final da perfusão extra-corpórea (T-4); 12h (T-12) e 24h após a conclusão do procedimento. As infusões, com duração de 3 horas, foram iniciadas 3 h antes do procedimento operatório.
RESULTADOS: Houve redução significativa da glicemia nos pacientes tratados com L-Ala-Gln durante o período intra-operatório (T-3 e T-4). O mesmo efeito não ocorreu nos pacientes do grupo salina. Como a taxa de infusão de insulina, administrada rotineiramente aos pacientes submetidos à cirurgia com circulação extracorpórea, foi constante em ambos os grupos durante o período intra-operatório, a redução da glicemia no grupo L-Ala-Gln não parece estar relacionada à insulina exógena.
CONCLUSÃO: O uso pré-operatório de L-Ala-Gln melhora o controle glicêmico em pacientes com obstrução coronariana, submetidos à revascularização miocárdica.
Descritores: Glutamina. Glicemia. Metabolismo. Doença da Artéria Coronariana. Procedimentos Cirúrgicos Cardiovasculares.

Introduction

Stress hyperglycemia is frequently seen in critically ill patients and is due to increased counterregulatory hormones (glucocorticoids, catecholamines, growth hormones, and glucagon), the effect of cytokines, and preexisting glucose intolerance[1]. In the past, up to the 1980s, no efforts were made to normalize blood glucose in acutely ill patients. Sustained hyperglycemia was interpreted as a potentially beneficial phenomenon, apt to increase substrate availability in the tissues and maintain urine output[2]. Tight glucose control below 110 mg/dL with insulin has been shown to exert anti-inflammatory effects in critically ill patients[3]. Recent studies have pointed out the negative effects of persistent hyperglycemia in cardiac surgery patients. Post-operative complications including localized or systemic infections have been identified[4-6].

Plasma glutamine level decreases at times of acute and/or critical illness in humans and is an independent predictor of outcome[7]. Studies often cited show efficacy for glutamine use in critically ill patients demonstrate improved mortality[8-10] and decreased length of hospital stay and intensive care unit costs[11].

Khogali *et al*.[12] investigated the effects of L-glutamine (0–20mM) on cardiac function of the isolated perfused working rat heart and concluded that glutamine may be suitable as a cardioprotective and rescue agent. The researchers affirmed that the protective effects of Gln would be mediated by maintenance of myocardial glutamate, ATP and phosphocreatine and prevention of lactate accumulation[12]. Considering that published experimental studies have shown that L-Ala-Gln improves glucose disposal[13], this paper is aimed at studying the possible effects L-Ala-Gln preoperative infusion in glycemic control in patients with coronary artery disease scheduled for coronary artery bypass grafting (CABG).

Methods

This prospective, randomized, controlled, double-blind study was approved by the local Ethics Committee (protocol #44/05, March 31, 2005) in compliance with the Helsinki Declaration of 1975, as revised in 2008 (World Medical Association www.wma.net/e/policy/b3.htm) and Resolution 196/96 of the Brazilian National Health Service (http://conselho.saude.gov. br/resolucoes/reso_96.htm). Written informed consent was obtained from all patients. Twenty-two elective patients (mean age: 63±8 years at the time of surgery) with coronary artery disease scheduled for CABG were randomly assigned to receive either L-Ala-Gln 20% solution (Dipeptiven – Fresenius Kabi) in saline 750 ml (Group L-Ala-Gln, n=11) or saline 1000 ml (Group Saline, n=11). The exclusion criteria were recognized diabetes mellitus, chronic renal or liver insufficiency and patients in use of systemic corticoid medication. Pre-operative blood samples were collected 3h before (T-1) and at the beginning of the surgical procedure (T-2). Intra-operative samples were collected immediately before the start (T-3) and the end of extra-corporeal perfusion (ECP), (T- 4). Post-operative samples were collected 12h (T-12) and 24h later (T-24). Infusions were started 3 h prior to the operative procedure and lasted 3 hours.

Surgical procedure

Conventional CABG was performed with single-stage venous cannula drainage, moderate systemic hypothermia, and antegrade or retrograde cold-blood cardioplegic solution. The patients were heparinized with an initial dose of heparin (3 mg/kg) and periodically supplemented with additional doses to maintain an activated clotting time of >480 s. At the end of the procedure, 1 mg of protamine per each milligram of heparin was given.

Patients received a continuous infusion of regular insulin throughout surgery and early postoperative period (24 h) via the infusion port of pulmonary artery catheter. Volumetric infusion pumps were used (Colleague with Continu-flo solution set, 2.8m, Baxter Healthcare Corp, Deerfield, IL). The infusion was prepared by mixing 5 mL of regular insulin (Humulin R, Eli Lilly), 100 units/mL in 500 mL of 0.9% saline to attain a final concentration of 1 U/mL. Initially, 50 mL of insulin was flushed through the solution set. For each patient, a fresh, unopened, refrigerated vial of insulin was used. In order to keep glycemia levels between 100-180 mg/dL insulin was administered to all patients in a fixed rate of 5 U/h during the intraoperative period. Blood glucose concentration was monitored hourly. Insulin infusion was discontinued when blood glucose levels reached <100 mg/dL. Raise of glycemia>100 mg/dL would trigger the resumption of the insulin infusion. In the early postoperative period (up to 48 h) insulin infusion was adjusted to maintain blood glucose concentration between 100 and 180 mg/dL.

Biochemical analysis

Insulin was assayed utilizing Roche/Hitachi Modular Analytics Laboratory Automation Systems, Modular P 800 Roche/Hitachi (Roche Diagnostics Corp., Indianapolis, USA). Blood glucose concentration was monitored by a glucometer (Accu-Chek Advantage®, Roche, Mannheim, Germany). Lactate concentrations were measured according to biochemical methods published elsewhere.[14]

Statistical methods

GraphPad 4.0 (GraphPad Software, San Diego, California, USA, www.graphpad.com) was used for computation and statistical analysis. Continuous variables were expressed as mean±SD, or median and interquartile range if distributions were skewed; a p value < 0.05 was considered significant. As results obtained involved multiple observations per patient, repeated variables in each group were analyzed by repeated measurement analysis of variance (ANOVA) and by two-way ANOVA.

Results

Results are presented in figures and tables. Blood glucose levels were significantly different in intraoperative period, comparing L-Ala-Gln treated patients with control values (Figure 1).

Insulin levels remained unchanged during the entire surgical procedure in both saline and L-Ala-Gln -treated patients (Figure 2).

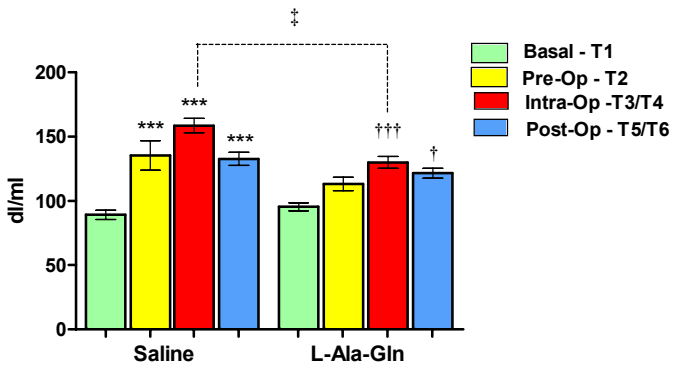

FIGURE 1 - Blood glucose concentrations (dl/ml) in Saline and L-Ala-Gln treated patients. Bars represent mean ± SD of blood glucose concentrations in saline-treated (control) patients and L-Ala-Gln treated patients. Glucose concentration was significantly decreased in L-Ala-Gln treated patients compared with controls during intra-operative (‡$p<0.05$) period by ANOVA test. Glucose concentrations increased significantly during surgical procedure pre-operative and intra-operative periods and remained elevated during post-operative period in both groups by Dunnett´s Multiple Comparison test.

***$p<0.001$, compared with basal values (saline group)
†††$p<0.001$, compared with basal values
†$p<0.05$, compared with basal values

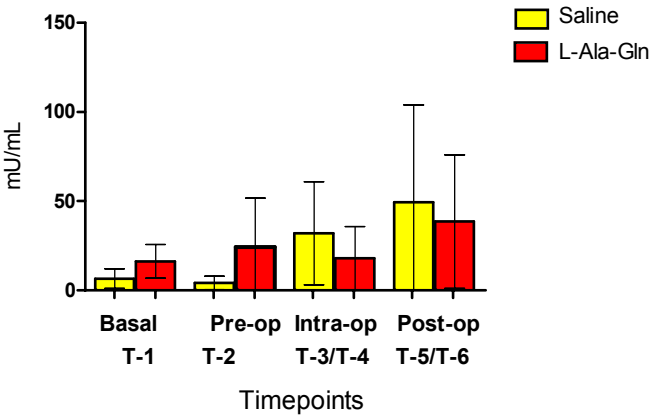

FIGURE 2 - Blood insulin concentrations (mU/ml) in Saline and L-Ala-Gln treated patients. Yellow bars and red bars represent mean ± SD of insulin concentrations in saline-treated (control) patients and L-Ala-Gln treated patients, respectively. Values were not different during the study by ANOVA test.

The concentration of blood lactate did not change with glutamine pretreatment (Table 1).

TABLE 1 - Plasma lactate concentrations (µMol/ml) in saline and L-Ala-Gln treated groups.

Timepoints	Saline			L-Alanyl-Glutamine		
	Mean	Median	IQR	Mean	Median	IQR
Basal	0.65	0.48	0.18-1.20	0.61	0.35	0.14-0.99
Preoperative	0.53	0.44	0.16-0.65	0.52	0.30	0.12-0.89
Intraoperative	0.41	0.37	0.16-0.53	0.37	0.20	0.13-0.59
Postoperative	6.41	6.02	4.40-8.30	4.76	4.65	1.73-6.96

Abbreviations : IQR, interquartile range

Discussion

The present study aimed to identify the effects of a nutraceutic dose L-Aln-Gln infusion (50g of the dipeptide) over 3 hours during the operative period, upon blood lactate and glucose concentrations in cardiac surgery patients.

Glutamine was infused over 3 hours preoperatively. The administration of L-ala-Gln by intravenous infusion during 3 hours was based on the fact that, in humans, administration of glutamine takes two hours to reach a steady state concentration in blood[15].

Hyperglycemia and insulin resistance mark the metabolic profile of stress response after surgery, and is more pronounced among diabetics[2]. For this reason, diabetic patients were excluded from our study.

L-Aln-Gln dipeptide in a 20% solution contains 13.46g of L-glutamine/100ml. This means that 33.6 g of L-glutamine were administered over 3 hours at a rate of 11.2 g of L-glutamine/hour. The average weight of patients who received the dipeptide infusion (group 2) was 59.8 kg. Therefore, patients received about 0.19g of L-glutamine/kg/hour. In various clinical studies, the use of glutamine (50-60g/day) for periods ranging from 4 hours to 30 days did not result in any deleterious effect[16]. Volunteers treated with high doses of glutamine (0.3 g/kg) orally in a single dose (bolus) and observed for 4 hours exhibited no signs of adverse effects[17]. In this study the amino acid was administered by continuous infusion. The dose used (11.2g/h) was 37% lower than that reported by Ziegler[17]. No adverse effects were observed.

The two primary mechanisms involved in triggering stress hyperglycemia are enhanced hepatic glucose production (increased gluconeogenesis) and decreased peripheral glucose use (insulin resistance)[2]. In our study the severe stress imposed by the surgical procedure lead to a significant increase in blood glucose levels during the surgical procedure in both groups, comparing pre-operative, intra-operative and post-operative periods with basal values (Figure 1). The significant decrease ($p<0.05$) in glycemia during the intra-operative period in L-Ala-Gln treated patients compared with saline-treated patients does not seem to be related to the exogenous insulin infusion considering that the infusion rate was constant in both groups. This difference in glycemia levels could be due to the ability of glutamine to reduce insulin resistance in critically ill patients. This has also been recently confirmed by Bakalar *et al.*[18] in an isotope study with hyperinsulinemic euglycemic clamp in severe trauma patients.

In the present study the concentration of blood lactate did not change with glutamine pretreatment. Contrary to our results, Alves *et al.*[19] found significant differences in venous blood lactate in patients with critical leg ischemia treated with L-Ala-Gln.

Some limitations to the current study were: 1) L-Ala-Gln infusion was limited to the preoperative period; 2) blood samples were collected from peripheral vessels and therefore subjected to hemodilution. There is a need for more randomized clinical studies aimed at elucidating the benefit of this nutritional strategy concerning a better glucose control in cardiac surgery patients. Nevertheless, the fact that there was a decrease in glucose concentration during the intraoperative period may be an indication of the potential therapeutic effect of preoperative L-Ala-Gln administration in critically ill heart surgery patients.

Conclusion

Preoperative use of L-Ala-Gln in nutraceutical doses improves glycemic control in patients with coronary artery occlusion, submitted to myocardial revascularization.

References

1. McMullin J, Brozek J, McDonald E, Clarke F, Jaeschke R, Heels-Ansdell D, Leppert R, Foss A, Cook D. Lowering of Glucose in Critical care: a randomized pilot trial. J Crit Care. 2007;22(2):112-8.
2. Annetta MG, Ciancia M, Soave M, Proietti R. Diabetic and nondiabetic hyperglycemia in the ICU. Curr Anaesth Critic Care. 2006;17:385-90.
3. Hansen TK, Thiel S, Wouters PJ, Christiansen JS, Van den Berghe G. Intensive insulin therapy exerts anti-inflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels. J Clin Endocrinol Metab. 2003;88(3):1082-8.
4. Capes SE, Dereck H, Malberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet. 2000;355(9206):773-8.
5. Bolk J, van der Ploeg T, Cornell JH, Arnold AE, Sepers J, Umans VA. Impaired glucose mechanism predicts mortality after myocardial infarction. Int J Cardiol. 2001;79(2-3):207-14.
6. van den Berghe G, Wouters P, Weekers F, Verwaest C,; Bruyninckx F, Schetz M, Vblasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001;345(19):1359-67.
7.Oudemans-van Straaten HM, Bosman RJ, Treskes M, van der Spoel HJ, Zandstra DF. Plasma glutamine depletion and patient outcome in acute ICU admissions. Int Care Med. 2001;27(1):84–90.
8. Griffiths RD, Jones C, Palmer TE. Six month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. Nutrition. 1997;13(4):295-302.
9. Griffiths RD, Allen KD, Andrews FJ, Jones C. Infection, multiple organ failure, and survival in the intensive care unit: influence of glutamine-supplemented parenteral nutrition on acquired infection. Nutrition. 2002;18(7-8):546-52.
10. Goeters C, Wenn A, Mertes N, Wempe C, Van Aken H, Stehle P, Bone HG. Parenteral L-alanyl-L-glutamine improves 6-month outcome in critically ill patients. Crit Care Med. 2002;30(9):2032-7.
11. Jones C, Palmer TEA, Griffiths RD. Randomized clinical outcome study of critically ill patients given glutamine-supplemented enteral nutrition. Nutrition. 1999;15(2):108-15.
12. Khogali SE, Harper AA, Lyall JA, Rennie MJ. Effects of L-glutamine on post-ischaemic cardiac function: protection and rescue. J Mol Cell Cardiol. 1998;30(4):819-27.
13. Borel MJ, Williams PE, Jabbour K, Levenhagen D, Kaizer E, Flakoll PJ. Parenteral glutamine infusion alters insulin- mediated glucose metabolism. JPEN J Parenter Enteral Nutr. 1998;22(5):280-5.
14. Hohorst HJ. D-Glucose-6-phosphate and D-fructose-6-phosphate. Determination with glucose-6-phosphate dehydrogenase and phosphoglucose isomerase. In: Bergmeyer HU (editor). Methods of enzymatic analysis. London: Verlag Chemie, Weinheim/Academic Press; 1963. p.134-8.

15. Mathews DE. Glutamine and glutamate kinetics in humans. In: Pharmacological nutrition immune nutrition. New York: W. Zuckschwerdt Verlag; 1995. p.68-76.
16. Garlick PJ. Assessment of the safety of glutamine and other amino acids. J Nutr. 2001;131(9 Suppl):2556S-61S.
17. Ziegler TR, Benfell K, Smith RJ, Young LS, Brown E, Ferrari-Baliviera E, Lowe DK, Wilmore DW. Safety and metabolic effects of L-glutamine administration in humans. JPEN J Parenter Enteral Nutr. 1990;14(4 Suppl):137S-46S.
18. Bakalar B, Duska F, Pachl,J, Fric M Otahal M Pazout J Andel M. Parenterally administered dipeptide alanyl-glutamine prevents worsening of insulin sensitivity in multiple-trauma patients. Crit Care Med. 2006;34(2):381-6.
19. Alves WF, Guimaraes SB, Vasconcelos PRC, Vasconcelos PRL de. Repercussions of l-alanyl-glutamine upon the concentrations of lactate and lactate dehydrogenase (LDH) in patients with critical ischemia of lower limbs subjected to distal revascularization. Acta Cir Bras. 2003;18(3):209-14.

Correspondence:
Paulo Roberto Leitão de Vasconcelos
Rua Professor Costa Mendes, 1608/3º andar
60430-140 Fortaleza – CE Brasil
Tel.: (55-85)3366-8083
Fax: (55-85)3366-8064
paulo.vasconcelos@ufc.br

Conflict of interest: none
Financial source: none

[1]Research performed at Walter Cantidio Hospital and Experimental Surgery Research Laboratory (LABCEX), Federal University of Ceara (UFC), Brazil.