Evaluation of the effectiveness of glutamine in different times of administration in patients undergoing cardiopulmonary bypass during elective cardiac surgeries: randomized controlled study

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Background
Although glutamine (GLN) is considered one of the pharmacological preconditioning proteins in cardiac surgeries, there is no consensus in literatures regarding the ideal time of administration. This randomized, double-blinded comparative study compared the effectiveness of GLN administration at two different time points in patients undergoing cardiopulmonary bypass.
Patients and methods
A total of 75 patients were randomly distributed into three equal groups: group 1 received GLN for 3 days preoperatively, group 2 received GLN at the day of surgery starting at the induction of anesthesia, whereas group 3, the control group, did not receive GLN.
Primary outcome included troponin I and creatine kinase-MB measured at 30 min, 6 h, 24 h, and 48 h after cardiopulmonary bypass (CPB). Secondary outcome included postbypass heart rate, blood pressure, ejection fraction by transesophageal echocardiography, systemic vascular resistance, ventilation time, incidence of arrhythmia and inotrope use, ICU and hospital stay, and mortality rate. The data were analyzed using statistical package for the social sciences (SPSS version 17), including χ^2-test for qualitative variables and analysis of variance test for quantitative variables. *P* value of less than 0.05 was considered statistically significant.
Results
There was a significant decrease in troponin I at 6, 24, and 48 h (*P*=0.03, 0.02, and 0.04, respectively), creatine kinase-MB at 24 and 48 h (*P*=0.04 and 0.04, respectively), incidence of inotrope usage (*P*=0.019), incidence of arrhythmias (*P*=0.02), and ICU stay (*P*=0.04), whereas significant increase in ejection fraction and blood pressure in GLN-treated groups (groups 1 and 2). The time of administration did not significantly affect the results between group 1 and group 2.
Conclusion
GLN enhances myocardial protection. The time of administration did not significantly affect the results, so administration at induction of anesthesia is well tolerated and feasible.

Keywords:
cardioprotection, glutamine, preconditioning, cardiopulmonary bypass

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Introduction

Despite the improvement in surgical techniques and the usage of cardioplegia and cardiac arrest, the risk of myocardial damage remains high after cardiac surgery in patients operated under cardiopulmonary bypass. This is owing to coronary microcirculation disturbances, apoptosis, and inflammation of myocardial cells [1].

Multiple studies including a meta-analysis of greater than 18 000 patients have shown that preoperative ischemia/reperfusion (I/R) injury during cardiac surgery [reflected by elevations in troponin I and creatine kinase (CK)-MB] increases morbidity and mortality. So, the protection of the myocardium following I/R injury is crucial in the preoperative period for these patients [2].

Preconditioning is a prophylactic activation of evolutionary natural endogenous protective response to stressful situations [3]. It is based on the fact that exposure to a nonlethal stimulus can activate a number of pathways that are designed to limit tissue injury. These pathways enhance heat shock proteins (HSPs), cyclooxygenase (COX-2), antiapoptotic factors, and antioxidant enzymes [4]. Preconditioning is the most powerful cardioprotective intervention ever known [5]. The clinical use of preconditioning was first described in cardiac surgery, by intermittent cross-clamping of

the aorta before cardioplegic arrest, but this technique was limited by the concerns regarding repeated manipulation of an atherosclerotic aorta and potential cerebral embolization. So, finding a clinically acceptable strategy to induce preconditioning or recruit the protection associated with it has proved elusive [6]. Many proteins have been examined for cardioprotection especially HSP72, COX-2, and nitric oxide synthase. Upregulation of COX-2 can be induced by drugs such as opioids and inhalational anesthetics [7,8].

Previous data indicated that the nonessential amino acid glutamine (GLN) can protect against myocardial injury by the induction of HSPs (specially HSP 25 and HSP 70) and COX-2 expression by the myocardial cells [3,9–12]. An additional mechanism of GLN protection is the enhancing of myocardial glutathione, ATP, and glutamate (the major stress substrate for stressed myocardium) after I/R injury [13,14]. HSPs are intracellular proteins found in every cell in the body and are one of the common underlying factors in all protective areas of GLN pretreatment, where their function is to guide the folding of newly synthesized proteins and to ensure continual guidance of damaged proteins toward the proteasome for destruction [15]. GLN also increases COX-2 expression and enhances levels of prostacyclin [7]. Prostacyclin is a vasodilating prostaglandin and is the most potent inhibitor of platelet aggregation; this reduces the no-reflow phenomenon during reperfusion and improves coronary flow. Prostacyclin also reduces after load and inhibits the activation of polymorphs [16].

The preoperative intravenous supplementation with GLN has been shown to attenuate the systemic inflammatory response to cardiopulmonary bypass in a rodent model [17].

The available data have shown that GLN can protect against myocardial cellular and organ injury *in vitro* and *in vivo* [17–19]. In our study, we investigated the protective effect of GLN in reducing morbidity and mortality at two different times in patients undergoing cardiopulmonary bypass.

Aim

This randomized double-blinded study was conducted to examine the effectiveness of GLN in protection of the myocardium in patients undergoing elective cardiopulmonary bypass surgeries comparing the administration for 3 days preoperatively with that at the induction of anesthesia in the day of surgery.

Patients and methods

The study was done on adult patients undergoing elective cardiac surgery with cardiopulmonary bypass after obtaining written informed consent and approval from the local ethical committee. Patients were recruited between December 2012 and August 2014, and their ages ranged from 32 to 59 years. Depending on a previous study and using Epi Info Version 7. [computer program]. Atlanta, Georgia (US): Centers for Disease Control and Prevention, licensed as public domain. Microsoft Excel 2010 running on Windows 7, Included in microsoft Office 2010, the sample size was 25 patients in each group at 80% power, 95% confidence interval, and *P* value less than 0.05. The exclusion criteria were as follows: patients with left ventricular ejection fraction (EF) less than 50%, onset of myocardial infarction (MI) less than 3 months, persistent elevation of TROP I and CK-BM level, emergency surgery, persisting kidney or liver dysfunction, or other comorbid conditions such as drugs or alcoholic abuse, HIV, and hepatitis C or B.

Patients were numbered according to their operative date, and their orders were randomized using a computer-generated random numbers and assigned into three equal study groups. Assignment to study protocol was directly submitted to the staff responsible for preparing the study solutions, who was not included in further handling of the data.

To ensure blindness, all groups received 200 ml of normal saline solution during 3 days before surgery and during the day of surgery starting at the induction of anesthesia:

(1) Group 1, 0.4 g/kg/day of *N*(2)-l-alanyl-l-glutamine (Dipeptiven 20%; Fresenius kabi; Dipeptiven ®; Fresenius kabi, Homburg, Germany) was added to patient's solution that was to be administered 3 days before the surgery.
(2) Group 2, 0.4 g/kg/day of *N*(2)-l-alanyl-l-glutamine (Dipeptiven) was added to patient's solution that was to be administered at the induction of anesthesia.
(3) Group 3 was the control, which took their solutions without adding GLN.

Volumes of study solutions were subtracted from the total body requirements for all patients. The patients and the staff providing patient care were blinded to the study protocol.

Anesthetic management

Patients were premedicated with 2 mg lorazepam orally at the night of the operation. In the operating room,

patients received O_2 through a face mask at a flow rate of 3–5 l/min before insertion of two large-bore peripheral cannulas and administration of 3–5 mg midazolam. Patients were monitored by five leads ECG, pulse oximeter, and arterial pressure transducer. Anesthesia was induced using 500–1000 μg fentanyl+2 mg/kg propofol titrated to effect, and then endotracheal tube was inserted after administration of 0.1 mg/kg pancuronium. The lungs were ventilated with a tidal volume of 8 ml/kg, FiO_2 of 0.6 in an air mixture, and ventilatory rate adjusted to maintain a $PaCO_2$ pressure of 32–36 mmHg.

After insertion of the tube and stabilization of ventilation, nasopharyngeal temperature probe, urinary catheter, central venous catheter, and transesophageal echocardiography (TEE) probe (Vivid 7imaging system; GE Healthcare, Amersham, Sweden) were inserted.

Anesthesia was maintained with continuous intravenous infusion of 1 μg/kg/h fentanyl, 1 mg/kg/h propofol, 0.1 mg/kg/h pancuronium, and supplemented with isoflurane as required.

Before the initiation of cardiopulmonary bypass (CPB), heparin, 3–5 mg/kg, was administered to achieve activated clotting time greater than 400 s. Activated clotting time level was checked regularly every 20–30 min and if needed, additional 5000–10 000 U of heparin was given. CPB was performed using nonpulsatile pump and membrane oxygenator (COBE Excel; Lakewood, Colorado, USA) with flow rates of 2.0–2.4 l/min/m^2 to maintain a mean perfusion pressure of 60–80 mmHg with mild hypothermia (33–34°C nasopharyngeal), α-stat management of pH, and hematocrit greater than 20%. Myocardial protection was achieved with intermittent antegrade and occasionally retrograde blood cardioplegia.

Active warming was started 15–20 min before the anticipated removal of the aortic cross-clamp. After the aorta was declamped, the heart was defibrillated, if necessary, and rescue medication (magnesium, lidocaine, amiodarone) and epicardial pacing to achieve a moderately elevated heart rate (>80 beats/min) were used at the discretion of the anesthesiologist. The predefined hemodynamic targets were as follows: mean arterial blood pressure greater than 60 mmHg, systemic vascular resistance (SVR) greater than 800 dyne s/m^5, CI greater than 2.5 l/min/m^2, and SVO_2 greater than 70%. Cardiovascular pharmacologic support therapy was used to achieve these predefined values: epinephrine (0.05–0.2 μg/kg/min) was the standard inotropic support. In the case of low cardiac output (COP) during or immediately after weaning from CPB, milrinone was added (loading dose 50 μg/kg over 10 min, followed by a continuous infusion of 0.5 μg/kg/min). Vasopressor support (0.05–0.2 μg/kg/min norepinephrine) was used if SVR was less than 800 dyne s/m^5 or when intravenous milrinone was used. If weaning was claimed successful, administration of protamine 1 mg/100 U heparin and decannulation was started. If weaning attempt failed in spite of cardiovascular pharmacologic support therapy, CPB was again resumed and an intra-aortic balloon pump was inserted.

Clinical data collections

Demographic data and preoperative and postoperative follow-up characteristics were reported and analyzed.

The primary outcomes were biochemical measurements for troponin I and CK-MB obtained from venous blood samples. Both markers were determined using enzyme-linked florescent assay technique (before anesthesia and 30 min, 6 h, 24 h, and 48 h after CPB). Troponin I was determined by VIDAS Troponin I ultra (normal range <0.01). CK-MB was determined by VIDAS CK-MB (normal range 0–4.9).

The secondary outcomes were hemodynamic measurements immediately after weaning off cardiopulmonary bypass and postoperative patients outcomes. Hemodynamic measurements included heart rate, mean arterial pressure (MAP), central venous pressure (CVP), EF, and SVR.

These measurements were detected by using central venous catheter, arterial catheter, standard ECG, and TEE. SVR was calculated according to the following equation: $SVR=(MAP\text{-}CVP_{mmHg})\times 80/$ cardiac output.

Patients' medical record provided the baseline EF, which was examined preoperatively by transthoracic echocardiography in cardiology department at the time of hospital admission. However, postbypass EF was obtained by intraoperative TEE performed by a cardiologist specialized in TEE who attended the operation according to the protocol followed in our hospital and was blinded to the allocation groups. The TEE examination included a midesophageal, four-chamber view, a short axis transgastric view at the midpapillary level, and color flow Doppler imaging of all the valves. The examination was obtained after induction of anesthesia, before CPB and immediately after CPB.

Postoperative patients' outcome included ventilation time (defined as the time between admission to ICU and extubation), mortality (defined as death occurring within hospitalization period), incidence of recent arrhythmia, incidence of inotrope use, and durations of ICU and hospital stay.

Statistical analysis

Data collected were coded, entered, and analyzed using Microsoft Excel software and then imported into statistical package for the social sciences (SPSS) 17 for Windows (SPSS Inc., Chicago, Illinois, USA). According to the type of data, the following tests were used to test differences for significance: differences between frequencies (qualitative variables) in groups were compared by χ^2-test, and differences between mean (quantitative variables) in groups were compared by analysis of variance test. *P* value was set at less than 0.05 for significant results.

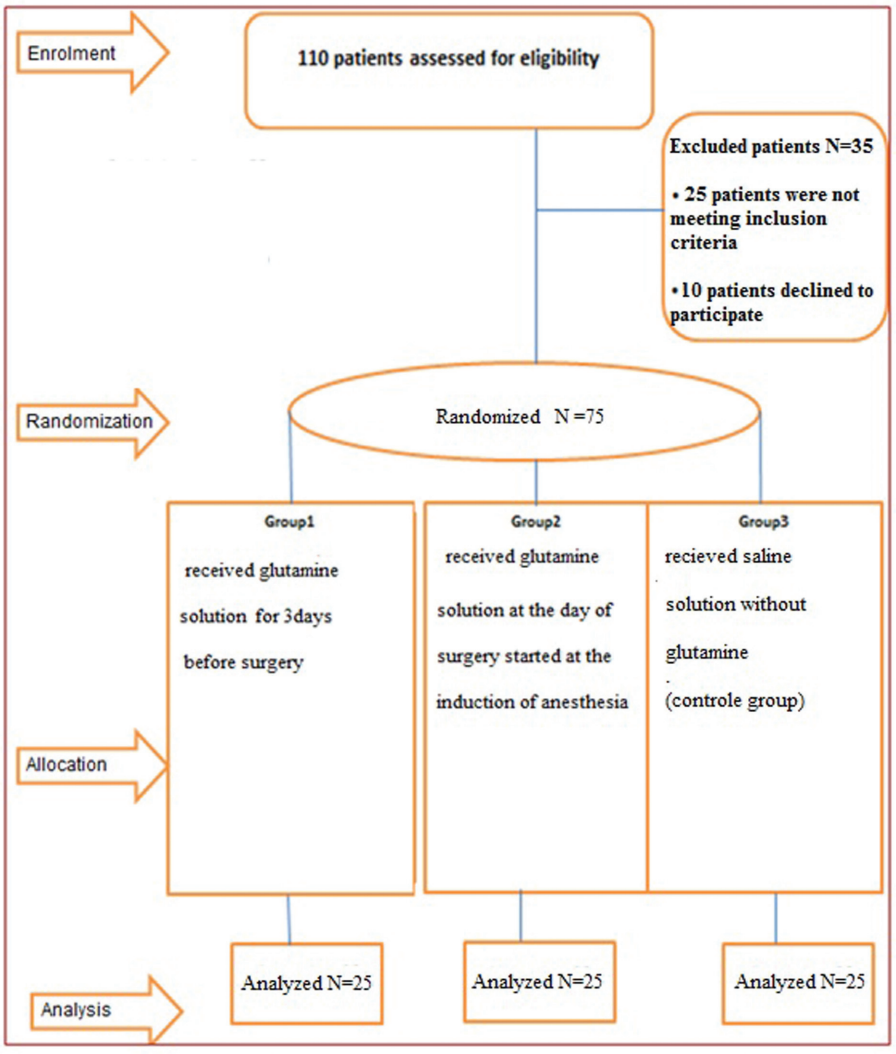
The study design was summarized according to Consolidated Standards of Reporting Trials (COSORT), as stated in Fig. 1.

Results

After fulfilling the inclusion criteria for this study, 75 patients were classified randomly into three groups. The baseline characteristics of patients in the three groups, including age, sex, weight, EF, pump time, aortic cross clamp time, and incidence of preoperative arrhythmia, showed no significant difference (Table 1).

There was no statistically significant difference in the baseline cardiac markers, either troponin I or CK-MB, among the groups. However, as shown in Table 2, the cardiac enzymes increased substantially toward the maximum at 6 h after bypass. After this point, the plasma concentration of the markers declined in the three groups. Patients in group 3 had significant

Figure 1



Study design (CONSORT diagram).

increase in troponin I at 6 h, 24 h, and 48 h and in CK-MB at 24 h and 48 h after bypass compared with group 1 and group 2. No significant difference was found in cardiac markers between group 1 and group 2.

Regarding the hemodynamic characteristics after bypass, patients in group 3 had statistically significant lower left ventricle EF and lower blood pressure than the other two groups. Other findings of hemodynamics showed insignificant difference among the three groups (Table 3).

The clinical course and outcome are summarized in Table 4. There was a case of intraoperative mortality in group 1 and another case of mortality that occurred 24 h after surgery in group 3, with no significant difference in the mortality rates among the three groups. The ventilation time did not differ significantly among the three groups, but there was significant higher incidence of arrhythmias and higher numbers of patients who needed postoperative inotropic support in group 3 compared with the other two groups. The ICU stay was significantly higher in group 3, with no statistically significant deference in hospital stay in the three groups.

Table 1 Patients' basic characteristics

	Group 1 (*N*=25)	Group 2 (*N*=25)	Group 3 (*N*=25)	*F*	*P*
Male	15	13	11	0.6	0.3
Female	10	12	14	0.7	0.2
Age	45±13.1	47±12	48±11.9	1.2	0.1
Weight	69±15	74±14	70±16	0.8	0.2
Preoperative EF	63±14.7	62±13.9	64±15	0.5	0.4
Preoperative arrhythmia (number of patients)	1	0	1	2.5	0.09
Pump time	150±40	144±53.9	156±38.8	0.4	0.6
Aortic cross clamp time	126±20	118±36.3	127±23.7	0.8	0.2

EF, ejection fraction.

Discussion

Our findings in this study indicate that GLN administration significantly reduces myocardial injury after cardiobypass. This is confirmed by decrease in level of myocardial markers, CK-MB and troponin I. Troponin I is considered to be the most specific marker of myocardial injury [20], and it has proven to be of great value to predict adverse cardiovascular events [21]. The creatine phosphokinase MB fraction (CK-MB) has long been considered a marker for the diagnosis of acute myocardial infarction (AMI), but it is less sensitive and specific, compared with the cardiac troponins [21]. With the availability of cardiac troponins, the dosage of CK-MB mass may be dispensable for prognostic evaluation. However, in the absence of troponins, CK-MB mass is an acceptable alternative [22]. So we decided to examine both enzymes in this study to evaluate myocardial injuries.

Pretreatment with GLN enhances HSP72 expression, which is a potential mechanism for attenuating the expression of myloperoxidase enzyme, a sensitive predictor for MI, and reducing the levels of CK released following both the ischemia and the reperfusion phases [23]. In addition, GLN has been shown to prevent glutathione depletion and improve antioxidant status in the heart [24]. Furthermore, it can prevent ATP depletion following myocardial I/R injury [25] and promote cardioprotective effects when used either parenteral or enteral [11,26–29].

The perioperative administration of GLN in patients with ischemic heart disease following cardiopulmonary bypass showed reduction in troponin I and improvement in myocardial function [30].

Table 2 Cardiac markers

	Prior to anesthesia	30 min	6 h	24 h	48 h
Troponin I					
Group 1	0.002±0.001	0.008±0.001	0.06±0.001	0.05±0.001	0.009±0.002
Group 2	0.002±0.001	0.0079±0.001	0.08±0.002	0.06±0.001	0.01±0.001
Group 3	0.0021±0.006	0.0085±0.004	0.16±0.04	0.12±0.05	0.07±0.003
F	0.14	0.4	3.6	4.1	3.3
P	0.91	0. 6	0.03*	0.02*	0.04*
CK-MB					
Group 1	1±0.2	5.1±0.9	6.2±0.9	5±0.8	3.2±0.9
Group 2	1.2±0.3	5.4±0.3	6.3±1.1	5±1	3.5±0.8
Group 3	0.9±0.32	5.9±0.3	7.8±1	7.4±1	5.8±2.4
F	2.5	2.75	2.9	3.3	3.3
P	0.09	0.07	0.06	0.04*	0.04*

CK, creatine kinase. *Significant at P value < 0.05.

Table 3 Hemodynamic characteristics

	Group 1	Group 2	Group 3	*F*	*P*
HR (beats/min)	100±10	96±6.5	95±5	3	0.07
Mean BP (mmHg)	68±6	69±6	64±4	5.966	0.004*
Ejection fraction (left ventricle)	60±6.5	59±9	54±7	4.499	0.014*
Central venous pressure(cm H_2O)	7±2	7.5±2.1	8±1.9	2.5	0.09
Systemic vascular resistance (dynes/s/cm^5)	1300±96	1260±80	1230±101	3.1	0.07

BP, blood pressure; HR, heart rate. *Significant at *P* value < 0.05.

Table 4 Outcomes

	Group 1	Group 2	Group 3	*F*	*P*
Ventilation time (h)	8	7	8.5	0.22	0.8
ICU stay (h)	34±6	32±7	38±8	4.698	0.01*
Hospital stay (days)	10±2	11±2.5	11±3	1.298	0.279
Mortality (number of patients)	1	0	1	2.5	0.09
Arrhythmia (number of patients)	3	2	10	4.1	0.02*
Number of patients on inotropes	8	9	17	7.86	0.019*

*Significant at *P* value < 0.05.

Alexandra *et al*. [28] studied GLN when given orally 3 days preoperatively to patients undergoing cardiac surgeries, requiring cardiopulmonary bypass, and found reduction in cardiac enzymes and improvement of postoperative outcome. Bakalar *et al*. [27] in their study found that alanyl-GLN, the parenteral form of GLN, was shown to decrease the severity of I/R injury in patients with multiple trauma.

The increased EF after bypass shown in our study is supported by a previous in-vitro study done by Wischmeyer and his colleagues on isolated cardiomyocytes, which demonstrated that GLN supplementation before I/R injury markedly reduced cell death. This protection was accompanied by return of contractile function in all GLN-treated cells compared with the control cells. Moreover, they found significant increase in HSP72 levels in the GLN-pretreated group [13]. These findings are also consistent with previous clinical study in which preoperative GLN significantly enhanced cardiac output and increased cardiac and stroke index following cardiopulmonary bypass [30].

The improvement in EF in both GLN-treated groups shown in our results may explain the lower number of patients who needed inotropic support during and/or after weaning off cardiopulmonary bypass.

In a post-hoc analysis study on patients undergoing isolated CABG for acute coronary syndrome, intravenous glutamate was associated with a significant reduction in the risk of developing severe circulatory failure, needing intra-aortic balloon pump at weaning from CPB, and reduction in inotropic duration and needs [31].

In the current study, the pretreated patients showed lower incidence of postoperative arrhythmias in either group 1 or group 2. Takahashi *et al*. [32] concluded that elevated atrial HSP 70 enhanced by GLN has been associated with decreased postoperative arrhythmias.

Our result revealed prolonged ICU stay in nontreated series (group 3). Previous studies demonstrated that arrhythmias [33] and inotropic support [34] were considered as important independent predictors of prolonged ICU stay after cardiac surgeries. Intraoperative challenges play also a significant role in determining the length of ICU stay. These include factors such as inadequate revascularization, low cardiac output related to systemic inflammatory response syndrome, stunned myocardium, or inadequate myocardial protection during bypass [35].

The dose of GLN used in the current study (0.4 g/kg/day) was proven to have cardioprotective effects in patients following cardiopulmonary bypass [30]. The safety of this dose was examined in a study done on 44 preterm neonates who were given TPN supplementation for 15 days, and it concluded that GLN at this dose was safe even in preterm infants [19]. The timing of GLN administration differs among literatures [13,18,21,22,25,30,31,36]. Alexandra *et al*. [28] used three oral doses of GLN preoperative and Engel *et al*. [36] used three intravenous doses of GLN postoperative to prove the beneficial effect of GLN as a cardiac pharmacological preconditioning agent. Our results, however, revealed that there is no significant difference between group 1, in which alanyl-l-glutamine was initiated immediately after induction of anesthesia and sustained for 24 h postoperatively,

and group 2, in which patients received alanyl-l-glutamine for 3 days before surgery.

In agreement with our result, Wischmeyer *et al*. [18] proved that single dose of GLN can enhance HSP expression and improve myocardial function after I/R injury, so it can be used in settings where major clinical stress is anticipated.

Lomivorotov *et al*. [30] infused GLN perioperatively during the first 24 h after cardiac surgeries and concluded improved outcomes. Murphy *et al*. [37] demonstrated that single bolus of GLN preconditioning can protect against tourniquet-induced local and distant organ injury in a rodent I/R model.

The most critical period during cardiac surgery is the time of reperfusion when more microvascular injuries, increased permeability of capillaries and arterioles, more reactive oxygen species, and the imbalance inflammatory response can occur [38]. Data revealed administration of GLN takes 2 h to reach a steady state concentration in blood [39], so long-term administration does not have an additional benefit.

Conclusion

We concluded that intravenous GLN injection is a safe and available drug and can improve the outcome after cardiopulmonary bypass. No significant differences were reported in the results when GLN administration started 3 days before surgery compared with administration immediately after induction of anesthesia, but the latter is easy, feasible, and more convenient for the patients and the anesthetist.

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Conflicts of interest

There are no conflicts of interest.

References

1 Murphy GJ, Angelini GD. Side effect of cardiopulmonary bypass: what is the reality? J Card surg 2004; 19:481–488.

2 Domanski MJ, Mahaffey K, Hasselblad V, Brener SJ, Smith PK, Hillis G, *et al.* Association of myocardial enzyme elevation and survival following coronary artery bypass graft surgery. JAMA 2011; 305: 585–591.

3 McGuinness J, Neilian TG, Cummins R, Sharkasi A, Bouchier-Hayes D, Redmond JM. Intra venous glutamine enhances COX-2 activety giving cardioprotection. J Surg Res 2009; 152:140–147.

4 Bolli R. The late phase of preconditioning. Circ Res 2000; 87:972–983.

5 Bolli R, Becker L, Gross G, Mentzer R Jr, Balshaw D, Lathrop DA. Myocardial protection at a cross roads: the need for translation into clinicaltherapy. Circ Res 2004; 95:125–134.

6 Wang Y, Kodani E, Wang J, Zhang S, Takano H, Tang X, Bolli R. Cardio protection during the final stage of the late phase of ischemic preconditioning is mediated by neuronal NO synthase in concert with cyclooxygenase-2. Cric Res 2004; 95:84–91.

7 Shinmura K, Tang XL, Wang Y, Xuan YT, Liu SQ, Takano H, *et al.* Cyclooxygenase-2 mediates the cardio protective effects of the late phase of ischemic preconditioning in conscious rabbits. Proc Natl Acad Sci USA 2002; 97:10197–10202.

8 Tanaka K, Ludwing LM, Krolikowski JG, Alcindo D, Pratt P, Kersten J, *et al.* Isoflurane produce delayed preconditioning against myocardial ischemia and reperfusion injury: role of cyclooxygenase-2. Anesthesiology 2004; 100:525–531.

9 Wischmeyer PE. Glutamine: the first clinically relevant pharmacological regulator of heat shock protein expression? Curr Opin Clin Nutr Metab 2006; 9:201–206.

10 Sufit A, Weitzel LB, Hamiel C, Queensland K, Dauber I, Rooyackers O, Wischmeyer PE. Pharmacologically dosed oral glutamine reduces myocardial injury in patients undergoing cardiac surgery: a randomized pilot feasibility trial. J Parenter Entral Nutr 2012; 36:556–561.

11 Ugurlucan M, Erer D, Karatepe O, Ziyade S, Haholu A, Ugurlucan F, *et al.* Glutamine enhances the heat shock protein 70 expression as a cardioprotective mechanism in left heart tissues in the present of diabetes mellitus. Expert Opin Ther Targets 2010; 14:1143–1156.

12 Kim KS, Suh GJ, Kwon WY, Lee HJ, Jeong KY, Jung SK, *et al.* The effect of glutamine on cerebral ischaemic injury after cardiac arrest. Resuscit 2013; 84:1285–1290.

13 Wischmeyer PE, Vanden Hoek TL, Li C, Shao Z, Ren H, Riehm J, Becker LB. Glutamine preserves cardiomyocyte viability and enhances recovery of contractile function after ischemia reperfusion injury. J Parentral Nutr 2003; 27:116–122.

14 Khogali SE, Pringle SD, Weryk BV, Rennie MJ. Is glutamine beneficial in ischemic heart disease? Nutrition 2002; 18:123–126.

15 Benjamin I, McMillan D. Stress (heat shock) proteins: molecular chaperones in cardiovascular biology and disease. Circ Res 1998; 83: 117–132.

16 Thiemermann C, Zacharowski K. Selective activation of E-type prostanoid (3)-receptors reduces myocardial infarct size. A novel insight into the cardioprotective effects of prostaglandins. Pharmacol Ther 2000; 87: 61–67.

17 Hayashi Y, Sawa Y, Fukuyama N, Nakazawa H, Matsuda H. Preoperative glutamine administration induces heat shock protein 70 expressions and attenuates cardiopulmonary bypass-induced inflammatory response by regulating nitric oxide synthase activity. Circulation 2002; 106: 2601–2607.

18 Wischmeyer PE, Jayakar D, Williams U, Singleton KD, Riehm J, Bacha EA, *et al.* Single dose of glutamine enhances myocardial tissue metabolism, glutathione content and improves myocardial function after ischemia-reperfusion injury. J Parenter Entral Nutr 2003; 27: 396–403.

19 Lacey JM, Crouch JB, Benfell K, Ringer SA, Wilmore CK, Maguire D, *et al.* The effects of glutamine supplemented parenteral nutrition in premature infants. J Parenter Enteral Nutr 1996; 20:74–80.

20 Newby LK, Goldmann BU, Ohman EM. Troponin: an important prognostic marker and risk-stratification tool in non-ST-segment elevation acute coronary syndromes. J Am Coll Cardiol 2003; 41:31s–36s.

21 Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey Junior DE, *et al.* ACC/AHA 2007 Guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/NonST-Elevation Myocardial Infarction). Circulation 2007; 116:e148–e304.

22 Santos ES, Baltar VT, Pereira MP, Minuzzo L, Timerman A, Avezum A. Comparison between cardiac troponin I and CK-MB mass in acute coronary syndrome without ST elevation. Arq Bras Cardiol 2011; 96:179–187.

23 Prem JT, Eppinger M, Lemmon G, Miller S, Nolan D, Peoples J. The role of glutamine in skeletal muscle ischemia/reperfusion injury in the rat hind limb model. Am J Surg 1999; 178:147–150.

24 Leichtweis S, Ji L. Glutathione deficiency intensifies ischaemia-reperfusion induced cardiac dysfunction and oxidative stress. Acta Physiol Scand 2001; 172:1–10.

25 Perrault LP, Menasche P. Preconditioning: can nature's shield be raised against surgical ischemic-reperfusion injury? Ann Thorac Surg 1999; 68:1988–1994.

26 Lomivorotov VV, Efremov SM, Shmirev VA, Ponomarev DN, Lomivorotov VN, Karaskov AM. Glutamine is cardioprotective in patients with ischemic heart disease following cardiopulmonary bypass. Heart Surg 2011; 14:384–388.

27 Bakalar B, Duska F, Pachl J, Fric M, Otahal M, Pazout J, *et al.* Parenterally administered dipeptide alanyl glutamine prevents worsening of insulin sensitivity in multiple-trauma patients. Crit Care Med 2006; 34:381–386.

28 Sufit A, Weitzel LB, Hamiel C, Queensland K, Dauber I, Rooyackers O, Wischmeyer PE. Pharmacologicaly dosed oral glutamine reduces myocardial injury in patients undergoing cardiac surgery: a Randomized pilot feasibility trial. J Parenter Enteral Nutr 2012; 36:556–561.

29 Lauzier B, Vaillant F, Merlen C, Gélinas R, Bouchard B, Rivard ME. Metabolic effects of glutamine on the heart: Anaplerosis versus the hexosamine biosynthetic pathway. J Mol Cell Cardiol 2013; 5:92–110.

30 Lomivorotov VV, Efremov SM, Shmirev VA, Ponomarev DN, Lomivorotov VN, Karaskov AM. Glutamine is cardioprotective in patients with ischemic heart disease following cardiopulmonary bypass. Heart Surg Forum 2011; 14:E384–E388..

31 Vidlund M, Tajik B, Håkanson E, Friberg O, Holm J, Vanky F, *et al.* Post hoc analysis of the glutamics-trial: intravenous glutamate infusion and use of inotropic drugs after CABG. BMC Anesthesiol 2016; 16:541–549.

32 Takahashi N, Wakisaka O, Yoshimatsu H, Saikawa T. Induction of heat shock proteins prevent the arrhythmogenic substrate for atrial fibrillation. Int J Hyperthermia 2009; 25:641–646.

33 Reinelt P, Karth GD, Geppert A, Heinz G. Incidence and type of cardiac arrhythmias in critically ill patients: a single center experience in a medical-cardiological ICU. Intensive Care Med 2001; 27:1466–1473.

34 Osinaike BB, Okikilou B, Olusesin O. Prolonged intensive care unit stay after coronary artery bypass graft surgery: role of perioperative factors. Niger Postgrad Med J 2015; 22:213–216.

35 Michalopoulos A, Tzelepis G, Pavlides G, Kriaras J, Dafni U, Geroulanos S. Determinants of duration of ICU stay after coronary artery bypass graft surgery. Br J Anaesth 1996; 77:208–212.

36 Engel JM, Muhling J, Kwapisz M, Heidt M. Glutamine administration in patients undergoing cardiac surgery and the influence on blood glutathione levels. Acta Anethesiol Scand 2009; 53:1317–1323.

37 Murphy CG, Chen G, Winter DC, Bouchier-Hayes DJ. Glutamine preconditioning protects against tourniquet-induced local and distant organ injury in a rodent ischemia-reperfusion model. Acta Orthopaedica 2007; 78:559–566.

38 Carden DL, Granger DN. Pathophysiology of ischemia-reperfusion injury. J Pathol 2000; 190:255–266.

39 Mathews DE. Glutamine and glutamate kinetics in humans. In: Pharmacological nutrition immune nutrition. New York: W. Zuckschwerdt Verlag; 1995. 68–76.