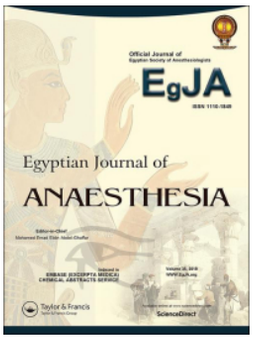

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Effects of preoperative intravenous glutamine administration on cardiac and renal functions in patients undergoing mitral valve replacement surgeries: A randomized double-blind controlled trial

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ABSTRACT

Background: Preoperative poor nutrition greatly raises the risk of complications and increases length of stay (LOS). Glutamine deficiency may impair immune functions, reduce myocardial adenosine triphosphate–adenosine diphosphate (ATP-ADP) substrate and decrease myocardial glutathione level. We evaluated the effects of preoperative glutamine administration in patients undergoing mitral valve replacement surgery upon cardiac and renal outcomes or hospital/ICU LOS.

Methods: This prospective randomized double-blinded study included 60 patients above 18 up to 60 years undergoing mitral valve replacement. For 3 days preoperatively, Group N patients received glutamine intravenously 0.4 g/kg/day while Group C patients received intravenous normal saline as placebo. The primary outcome was to assess the effects of glutamine on cardiac function as reflected on proBNP (brain natriuretic peptide) during 4 postoperative days. Secondary outcomes included renal function, vasoactive inotropic score, duration of mechanical ventilation, and hospital/ICU stays.

Results: Postoperative proBNP was significantly lower in Group N during the entire period. It was significantly decreased on the first postoperative day in both groups in comparison to the preoperative values. No significant changes were recorded regarding renal functions, and duration of mechanical ventilation between groups. Also, there was signifiacant difference between the two studied groups regarding the vasoactive inotropic score at the 12th, 18th, 24th and 48th hours with lower scores in Group N. ICU and hospital stays were significantly lower in Group N than Group C.

Conclusion: Short term of preoperative intravenous glutamine 0.4 g/kg/day decreased the postoperative proBNP level and hospital/ICU stays in mitral valve replacement surgery. No significant implication was reported upon postoperative human NGAL level or kidney functions.

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Glutamine; immunonutrition; cardiac function; brain natriuretic peptide; open heart surgeries

1. Introduction

Major surgical interventions disrupt the host's functional homeostasis and inflammatory responses, increasing the rate of postoperative complications and prolonging the length of hospital stay (LOS). Several investigators have argued that immunonutrition formulations supplemented with bioactive nutrients reduce inflammation, enhance healing of wounds and shorten hospital stay after surgeries [1].

It is clear that the immunonutrion-enriched nutrient formula is superior to the regular dietary intervention for promoting wound healing after surgeries, shortening length of hospital stay (LOS), and decreasing incidence of inflammation [2]. Regardless the advances in surgical interventions using the cardioplegia and cardiac arrest, the risk of myocardial injuries remains high following cardiac surgery in patients who underwent cardiopulmonary bypass. This is due to disturbances of coronary microcirculation, apoptosis, or inflammation of the myocardial cells [3].

Conditional amino acids are usually not essential (except in times of illness and stress), which include arginine, cysteine, glutamine, tyrosine, glycine, ornithine proline and serine. In certain pathological conditions, such as burns, traumas, total parenteral nutrition, or in physiological status during pregnancy and weaning, a number of non-essential amino acids (arginine, glutamine, glutamate, glycine, proline, taurine, and cysteine) have been found to become compulsorily essential. This change in the need for specific amino acids can be due in part to their effects on the immune system [4]. Glutamine is a conditional

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essential amino acid, which has a well-known protective effects on gastrointestinal tract mucosa through the enhancement of heat shock protein production which in turn reduces the effects of inflammatory-induced cytokine cellular damage [5]. Glutamine deficiency impairs immunity and gastrointestinal endothelial dysfunction [6].

Glutamine has beneficial immune functions related to cardiac protection after ischemia/reperfusion (I/R) in cardiopulmonary bypass (CPB); it increases myocardial adenosine triphosphate-adenosine diphosphate (ATP-ADP) substrate, prevents intracellular lactate accumulation, and enhances the accumulation of myocardial glutathione (GSH), a major stress substrate for the stressed myocardium, post-I/R injury [7].

Limited research has focused on preoperative immunonutrition through glutamine supplementation for cardiac patients undergoing cardiac surgery upon cardiac enzymes [8]. Accordingly, this study was constructed with its hypothesis focusing on the postoperative pro-Brain Natriuretic Peptide (proBNP) as a predictor of cardiac outcome following open heart surgery NT-proBNP reflected the grade of heart failure and proved to be useful indicator for evaluating heart failure. In cardiac surgery, it pointed out as independent indicator to predict postoperative outcomes [9]. Compared with other indicators, it seems to be equal to EuroSCORE but superior to ejection fraction [10].

Also, this study hypothesized that immunonutrition might protect the cardiac and renal functions in cardiac patients undergoing mitral valve replacement surgery. It could decrease the hospital and ICU stays with minimal complications.

2. Methods

This randomized double-blinded clinical study was conducted on adult patients scheduled for elective mitral valve replacement surgery under cardiopulmonary bypass (CPB) in Assiut University Hospitals after approval from the Medical Ethical Committee, Faculty of Medicine, Assiut University on 24 June 2018 (IRB17200167) and registered on ClinicalTrials.gov under the number NCT03445221. The provision of written informed consent was obtained from each patient before participation in the study.

Randomization and Blinding: Sixty adult patients prepared for elective mitral valve replacement surgery were randomized through a computer-generated table into two equal groups to receive the coded drugs. The anesthetic technique and outcome data were controlled by an anesthesiologist who was not included in the study drugs administration or the envelop coding. Neither the anesthesiologist assessing the study outcomes nor the patients themselves were aware of group assignment to ensure the blindness of the study.

The trial included patients of both genders, aged above 18 up to 60 years of ASA grade II-Ш, and undergoing elective mitral valve replacement surgery. Exclusion criteria included previous cardiac surgery, CPB time >120 minutes, patients with left ventricular ejection fraction less than 40%, advanced systemic disease, e.g.,, hepatic failure/cirrhosis, renal impairment (creatinine ≥3.5 mg/dl or dialysis), and/or diabetes.

2.1. Study groups

Group N: patients received preoperative glutamine in the form of DIPEPTIVEN® Dipeptiven-Fresenius Kabi – (N(2)-l-alanyl-L-glutamine 200 mg/mL) given by intravenous infusion of 0.4 g/kg daily for 3 days preoperatively at a rate of 0.1 gm/kg/h. Group C: patients received a placebo in the form of normal saline (NaCl 0.9%) given by intravenous infusion for 3 days before surgery.

2.2. Anesthetic management

An intravenous line was inserted, and premedication with intravenous midazolam 0.05–0.1 mg/kg was given in the preoperative holding area and then the patient was transferred to operative theatre where basic monitors (5-leads ECG, non-invasive BP, pulse oximeter) were attached to the patient. Under local anesthesia (lidocaine 1%), an arterial cannula was inserted after complete aseptic technique. In both groups, general anesthesia was induced with fentanyl in a dose of 1–2 µg/kg and propofol 1–2 mg/kg. Endotracheal intubation was facilitated with cisatracurium at a dose of 0.15 mg/kg. Mechanical ventilation then started and continued under volume-controlled mode for the maintenance of normocarbia. In the right internal jugular vein, a central venous line was introduced.

Anesthesia was maintained under isoflurane 1–2% in an oxygen-air mixture (1:1 ratio) using Datex-Ohmeda Aespire anesthesia machine (Madison WI 53707–7550 USA), infusion of fentanyl 1–2 µg/kg/h, and cisatracurium 1 µg/kg/h. Monitoring of the patient was continued as before induction and included peripheral O_2 saturation (SpO_2), end-tidal CO_2, electrocardiogram, invasive systemic blood pressure, central venous pressure, nasopharyngeal (core) body temperature, arterial blood gases, and urine output by the Carescape B650 device (GE Healyhcare Finland Oy). Median sternotomy was performed in all patients. Intravenous heparin in a dose of 3–4 mg/kg was given after doing the piercing suture of the aorta to achieve activated clotting time more than 450 s, and protamine sulfate was used for its reversal by the end of the procedure. After confirmation of activated clotting

time more than 450 s and placement of aortic and venous cannulae, the patient cardiopulmonary bypass was initiated to keep mean arterial blood pressure appropriate to the degree of hypothermia applied anesthesia was maintained during bypass period using propofol, fentanyl, and cisatracurium infusion. Custodiol HTK was delivered at 3–4°C, 20 ml/kg to a maximum of 2 L.

Data Management: Data collection included demographic data, vital signs (heart rate and mean arterial pressure) was recoreded at base line (before anesthesia induction),on the 2nd, 4th, 6th, 12th, 18th, 24th, and 48th hours after induction of anesthesia. Serum proBNP levels preoperatively and then on postoperative the first and fourth postoperative days. Vasoactive inotropic score [11] every 2 h during the first postoperative 6 h and then at 6 h intervals till the end of the first 48 h postoperatively. VIS_{max} was calculated as follows: (VIS = 100× epinephrine dose in [µg/kg/min]+ 100× norepinephrine dose in [µg/kg/min] + 10,000× vasopressin dose in [units/kg/min]+ dobutamine in [µg/kg/min]+ dopamine dose in [µg/kg/min] + 50× levosimendan dose in [µg/kg/min] + 10× milrinone dose in [µg /kg/min]) during the first 24 h. Monitoring kidney functions: through urine output in the first 2 days postoperatively. Sampling for Neutrophil Gelatinase-Associated Lipocalin level (NGAL) was done preoperatively and on the first and fourth postoperative days. Serum urea and creatinine were evaluated on the first and second postoperative days as its levels can be detected in the plasma of patients as early as 2 h, peak at approximately 6 h after injury and its levels remain elevated for as long as 5 days [12].

2.3. Outcome measures

The main outcome was to evaluate the effects of preoperative immunonutrition upon cardiac function through postoperative proBNP at one and 4 days. Secondary outcomes were to evaluate renal function including serum creatinine and NAGAL level, the vasoactive inotropic scoreduration of mechanical ventilation, and hospital and ICU stays. Any complication (e.g., heart failure, renal failure and side effects of glutamine as nausea, vomting and chills) throughout the whole study was recorded and managed accordingly.

Blood Sampling for NT-proBNP and Human NGAL analysis: Venous blood samples (1–1.5 ml) were collected into serum separator tubes, then centrifuged, stored at 2–8°C over 12 h for separation of the serum, then stored at −40°C. For the proBNP, the detection level started from 20 ng/L up to 35,000 ng/L. The inter-assay % CV was 5.0–4.0% in the range of 40.9–32,096 ng/L. For NGAL, the inter-assay CV was 6.5%; linearity from 0.156 −10 ng/mL [13].

2.4. Statistical analysis

Sample size was estimated with G*Power 3 software [14]. Based on previous studies [3–5], 60 patients (30 in each group) were essential to reach an effect size of 0.3 reductions in the serum level of pro-BNP, at 0.05 alpha error and 90% power of the study.

The collected data were coded, entered, and analyzed using the SPSS 26, for windows (SPSS Inc., Chicago, Illinois, USA). The Kolmogorov–Smirnov test was used to test the normality of the data. Data are presented as mean ± standard deviation or ratio. The differences between frequencies categorical data in groups were compared by the X^2-test. The difference between means (quantitative parametric variables) between groups was done through the unpaired *t*-test, whereas the comparison of such variables within the same group was attained through the paired *t*-test. *p*-Value <0.05 was considered statistically significant.

3. Results

A total of 67 patients were evaluated for eligibility, six of them were excluded due to bypass time >120 min, and one patient refused to participate. Sixty patients were enrolled in this study follow-up and finally analyzed (Figure 1). Their demographic data and clinical characteristics are shown in Table 1 with no significant difference in between.

Postoperative proBNP was significantly lower in the glutamine group than in the placebo group during the whole period. It was significantly decreased on the first postoperative day in both groups in comparison to the corresponding baseline preoperative values. Group C showed a significant increase in the proBNP on the fourth postoperative day in comparison to the corresponding preoperative value (Table 2).

Postoperative VIS was significantly lower in the glutamine group than in the placebo group at the 12th, 18th, 24th, and 48th hours only with *p*-values of 0.04, 0.03, 0.01, and 0.02, respectively (Table 3).

No statistically significant differences were observed among the two study groups regarding the mean arterial blood pressure. The heart rate readings showed statistically significant differences between both groups during the whole study period, but without any clinical implications (Table 4).

Renal functions showed no statistically significant differences between the studied groups concerning perioperative NGAL level, postoperative serum urea and serum creatinine levels, and urine output volume over the first and second postoperative days with *p*-values ˃0.05 (Table 5).

Hospital and ICU stays were significantly lower in the glutamine group than that in the placebo group (*p*-values of 0.006 and <0.001, respectively). However, the duration of postoperative mechanical ventilation

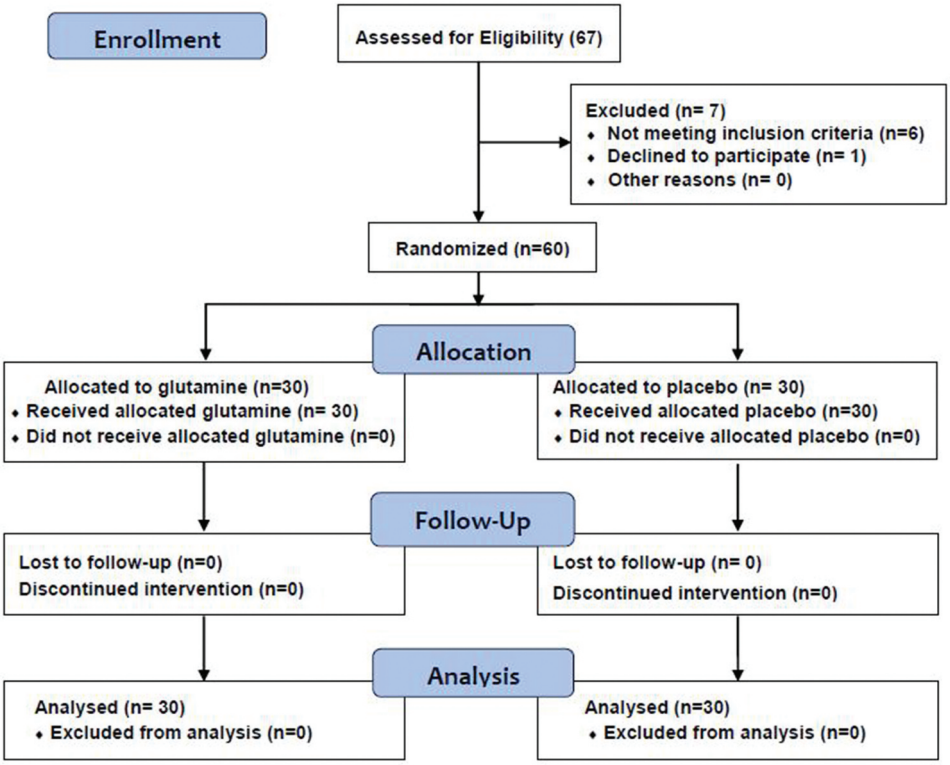

Figure 1. CONSORT flowchart of the studied groups.

Table 1. Demographic data and clinical characteristics in the two studied groups.

Variables	Group N (Glutamine group) (n = 30)	Group C (Placebo group) (n = 30)	p-Value
Age (years)	34 ± 8	30 ± 6	0.61
Gender (male/female)	13/17	14/16	0.5
Weight (kg)	75 ± 13	72 ± 12	0.4
Height (cm)	167 ± 9	167 ± 7	0.82
BMI (kg/m^2)	27 ± 3	26 ± 3	0.18
Duration of mechanical ventilation (h)	6 ± 2	6 ± 2	0.83
ICU stay (days)	3 ± 1	4 ± 1	<0.001*
Hospital stay (days)	7 ± 1	8 ± 1	0.006*

Notes: Data are presented as mean ± SD or ratio. There were no statistically significant differences between the two groups. *p-Value <0.05 is considered statistically significant.

Table 2. Perioperative serum proBNP in the studied groups.

ProB Natriuretic peptide (Pro BNP) level (ng/ml)	Group N (Glutamine group) (n = 30)	Group C (Placebo group) (n = 30)	p-Value
Preoperative proBNP	12 ± 3	22 ± 4	0.217
1st day postoperative proBNP	1 ± 0.5**	29 ± 5**	<0.001*
4th day postoperative proBNP	14 ± 3	34 ± 5**	0.003*

Notes: Data are presented as mean ± SD. p-Value <0.05 is considered statistically significant. (*) significant change from the baseline value. Independent t-test was used to compare the mean differences.

Table 3. Comparison of vasoactive inotropic score data between both study groups.

Vasoactive Inotropic score (VIS)	Group N (Glutamine group) (n = 30)	Group C (Placebo group) (n = 30)	p-Value
After 2 h	9 ± 1	11 ± 1	0.13
After 4 h	7 ± 1	9 ± 1	0.06
After 6 h	5 ± 0.8	7 ± 0.8	0.1
After 12 h	4 ± 0.5	5 ± 0.6	0.04*
After 18 h	2 ± 0.5	4 ± 0.6	0.03*
After 24 h	1 ± 0.4	3 ± 0.5	0.01*
After 30 h	0.9 ± 0.3	2 ± 0.4	0.07
After 42 h	0.4 ± 0.2	1 ± 0.3	0.07
After 48 h	0.2 ± 0.1	0.5 ± 0.2	0.02*

Notes: Data are presented as mean ± SD, number of patients. *p-Value < 0.05 is considered significant. Independent t-test is used to compare the mean differences.

Table 4. Postoperative mean blood pressure (mmHg) and Heart rate (beat/min) in the two studied groups.

	Group N (Glutamine group) (n = 30)	Group C (Placebo group) (n = 30)	p-Value
Postoperative mean blood pressure (mmHg)			
Baseline	81 ± 12	83 ± 12	0.7
MAP 2 h	81 ± 14	78 ± 14	0.3
MAP 4 h	82 ± 11	82 ± 10	0.9
MAP 6 h	82 ± 9	78 ± 8	0.1
MAP 12 h	80 ± 9	80 ± 10	0.6
MAP 18 h	78 ± 7	79 ± 7	0.7
MAP 24 h	80 ± 10	84 ± 10	0.08
MAP 48 h	79 ± 7	79 ± 7.5	0.93
Postoperative heart rate (beat/min)			
Baseline	86 ± 14	84 ± 17	0.67
HR 2 h	96 ± 13	88 ± 12	0.008*
HR 4 h	99 ± 14	89 ± 13	0.005*
HR 6 h	99 ± 12.6	89 ± 13	0.002*
HR 12 h	103 ± 12	90 ± 13	<0.001*
HR 18 h	102 ± 16	89 ± 10	0.001*
HR 24 h	103 ± 12	89 ± 9	<0.001*
HR 48 h	101 ± 14	89 ± 9	<0.001*

Notes: Data are presented as mean ± SD. *p-Value <0.05 is considered statistically significant. Independent t-test was used to compare the mean differences.

Table 5. Perioperative renal functions in the two studied groups.

Variables	Group N (Glutamine group) (n = 30)	Group C (Placebo group) (n = 30)
NGAL (ng/ml)		
• Preoperative	27 ± 2	33 ± 2
• 1st postoperative day	27 ± 2	34 ± 2
• 4th postoperative day	30 ± 2	30 ± 2
Serum creatinine (mmol/dl)		
• 24th hour	75 ± 36	90 ± 51
• 48th hour	76 ± 28	91 ± 41
Serum urea (mg/dl)		
• 24th hour	6 ± 5	7 ± 5
• 48th hour	6 ± 5	8 ± 4
Urine output (ml)		
• 24th hour	4316 ± 1097.6	4471 ± 975
• 48th hour	3726 ± 778	3806 ± 758

Notes: Data are presented as mean ± SD. There were no statistically significant differences between the two groups. p-Value <0.05 is considered statistically significant. Independent t-test was used to compare the mean differences. NGAL, neutrophil gelatinase-associated lipocalin level.

showed no statistically significant difference between both groups and p-value of 0.83 (Table 1)

No recorded complications were detected during the whole duration of study. No mortality was detected over the 30 postoperative days.

4. Discussion

The study involved 60 adult patients of both genders ASA I–III who underwent mitral valve replacement surgery. It showed that preoperative glutamine has a good impact on cardiac performance, in the form of significantly lower postoperative ProBNP level, lower vasoactive inotropic score, and shorter ICU or hospital stays. No significant effects were detected regarding the hemodynamic parameters and renal outcomes.

It is well known that glutamine supplementation in patients undergoing cardiac surgery offers favorable effects. preservation of myocardial glutamine during cardiopulmonary bypass (CPB) maintains mitochondrial high energy phosphate production. Also, myocardial glutamine availability supports glycolysis and prevents lactic acid accumulation during the ischemia reperfusion cycle [7].

Tostado and coworkers found that glutamine supplementation is advantageous in cardiac surgery patients as it increased the intracellular glutathione levels which have a well-known antioxidant effect. It minimizes myocardial injury following coronary remodeling under CPB [15]. Myocardial protection after ischemia–reperfusion can be attained by glutamine supplementation via increasing adenosine triphosphate-adenosine diphosphate substrate in myocardial tissues, preventing the accumulation of intracellular lactate and increasing myocardial glutathione [7]. The deleterious inflammatory response can occur with the use of CPB which slows recovery from surgery, increases infection rate, and cause damage to other body organs [16].

The results of this study are in line with Lomivorotov et al., who concluded a cardiac protective effect of glutamine by using troponin level reduction after coronary artery bypass grafting under CPB on the second postoperative day and at 24 h intervals. Their study was randomized and included 50 patients, and 25 patients received intravenous glutamine at a dose of 0.4 g/kg. The systemic vascular resistance index decreased significantly in the study group. Postoperative complications or mortality showed no

significant differences between groups [7]. Sufit et al. demonstrated that preoperative oral glutamine (37.5 g/day) for 3 days in surgeries with CPB other than artery bypass grafting, the postoperative TROP-I, CPK, and CPK-Mb levels decreased significantly at 24,48,72 h [17].

Regarding the use of perioperative proBNP changes as a primary endpoint of our study; NT-proBNP reflects the grade of cardiac dysfunction. It can predict postoperative outcomes in cardiac surgery [9]. NT-proBNP has a validity equal to EuroSCORE and more than ejection fraction. It was used in CABG, surgery for aortic stenosis, and percutaneous coronary intervention [10].

NT-proBNP in combination with EuroSCORE II is more effective as a prognostic tool in CABG patients with the cut-off point of NT-proBNP level being 1028 pg/ml. Patients with aortic or mitral stenosis had higher pre-operative levels than coronary artery diseases [10]. Another significant factor affecting proBNP level was kidney function [18] which was not affected in our study.

This study's results regarding the reduced ICU and hospital stays in the glutamine group agree with several clinical trials that carried the same perspectives. Several studies described that perioperative enteral or parenteral immunonutritional formulas have a role in improving postoperative results as reducing complications postoperatively and shortening the length of stay [19,20]. Other research works demonstrated that immunonutrition has the ability to improve the patients' immunity, reduce infection, and shorten the hospital stay after major surgeries, such as gastrointestinal surgery and liver transplantation [21].

Zhang et al. concluded that immunonutrition reduced the incidence of postoperative adverse effects and shortened the hospital stay in a meta-analysis with a total of 805 patients undergoing hepatectomy from 8 RCTs, in which 402 patients was given immunonutrition and 403 did not [19]. Another meta-analysis done by Waitzberg et al. included patients undergoing major surgeries (abdominal, cardiac and head and neck). They prescribed immunonutrition and they recorded lower incidince of wound infection and a decreased hospital stay whatever the time of immunonutrition administration but no effects were noticed on postoperative mortality [22].

The systematic review done by Tao et al. reported that glutamine can reduce infection and duration of mechanical ventilation, and with low level of evidence for a shortened hospital stay, in surgical patients [23]. However, some studies demonstrate no reduction in postoperative complication, LOS, mortality, or morbidity with the use of perioperative immunonutrition [24,25]. In well-nourished patients, some studies demonstrate only a reduction in the infectious complications with no cost-effectiveness advantages [25,26]. Few trials on immunonutrition suggested that the risk of death in the critically ill has been increased [27]. Oldani et al. found no difference between the glutamine and the placebo group for hospital and ICU mortality, or rate of infections in a meta-analysis included 30 RCTs in ICU patients [28].

5. Conclusion

Short-term preoperative intravenous infusion of glutamine 0.4 g/kg daily for 3 days in adults, ASA I–III patients undergoing mitral valve replacement surgery significantly decreased the postoperative proBNP level and length of hospital/ICU. Postoperative vasoactive inotropic score was significantly lower in the glutamine group than in the placebo group. However, no significant implication was detected regarding the postoperative human NGAL, kidney function and duration of mechanical ventilation. No serious adverse effects were observed during the entire study period, and no mortality was reported over the following 30 postoperative days.

6. Limitations

The limitations of this study might be the small sample size, involving only mitral valve replacement surgeries, short time of postoperative follow-up, and lack of serial measurement of serum ProBNP and NGAL levels. Cardiac enzymes were better to be investigated as well. We recommend further multicenter studies with a larger sample size to reach the conclusion of this study. In addition to using oral glutamine formulas to investigate the malnourished patients, and to evaluate different types of surgical procedures.

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Disclosure statement

The authors declared no conflict of interest with any financial organizations regarding the materials discussed in their manuscript.

Authors' contributions

Hany Ahmad Ibrahim Elmorabaa: supervision and critical revision of the manuscript. Mohamed F. Mostafa: design the study, writing and editing the manuscript. Emad Zarief Kamel: study design, data entry and statistical analysis. Mohammed Mahmoud Mostafa: surgical procedures and helped in patients' admission and study conduct. Ragaa Herdan: data revision and writing the manuscript.

Mohamed Ismail Seddik: helped in the laboratory measurements. Mostafa Hassanien Bakr: helped in search online and writing the manuscript. Ramy Mostafa Abd El Gawad: This author helped conduct the study and data collection.

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