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Effect of Perioperative Glutamine Supplementation on Acute Kidney Injury in Infants Undergoing Elective Cardiac Surgery: A Randomized Controlled Trial

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Abstract

Objective: Acute kidney injury (AKI) is a frequent and serious complication in infants after cardiac surgery. Glutamine (GLN), a conditionally essential amino acid, has demonstrated renoprotective potential in animal models and has been shown to attenuate biomarkers of kidney damage in high-risk patients undergoing cardiac surgery. However, whether these renoprotective benefits extend to pediatric patients remains unknown. **Methods:** We conducted a single-center, randomized, double-blind, placebo-controlled trial in infants and young children younger than 3 years undergoing cardiac surgery with cardiopulmonary bypass. Ninety-four patients were randomly assigned to receive intravenous alanyl-glutamine (0.4 g/kg/day, $n = 47$) or 0.9% saline placebo ($n = 47$), administered from anesthesia induction and continued for 4 consecutive days (the day of surgery and the first 3 postoperative days). The primary outcome was the incidence of AKI within 72 h postoperatively, defined according to the KDIGO criteria. Secondary outcomes included the requirement for peritoneal dialysis (PD), diuretic use, serum creatinine (Scr), neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, procalcitonin, and the lengths of ICU and hospital stay. **Results:** The incidence of KDIGO-defined AKI was lower in the GLN group than in the control group (14.9% vs. 40.4%; $p = 0.010$). Among the prespecified secondary outcomes, the requirement for PD (0% vs. 12.8%; $p = 0.026$) and diuretic use (6.4% vs. 23.4%; $p = 0.040$) were also lower in the GLN group. Postoperative NGAL concentrations were lower in the GLN group at 24, 48, and 72 h ($p < 0.050$ for each time point). No significant differences were observed in the lengths of ICU or hospital stay. **Conclusions:** In this single-center trial, perioperative GLN supplementation was associated with a lower incidence of postoperative AKI, a lower requirement for PD, and less diuretic use in infants undergoing elective cardiac surgery. These exploratory findings support a possible renoprotective role for GLN in this high-risk population but require confirmation in larger multicenter trials before adoption into clinical practice.

Keywords: glutamine; infant; acute kidney injury; congenital heart disease; cardiopulmonary bypass

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1. Introduction

Acute kidney injury (AKI) is among the most common and serious complications following cardiac surgery with cardiopulmonary bypass (CPB), affecting approximately 12–43% of adults and 40–62% of neonates and infants [1,2]. Cardiac surgery-associated AKI

(CS-AKI) is independently associated with increased postoperative morbidity and mortality, prolonged mechanical ventilation, and extended intensive care unit (ICU) and hospital stays [3–5]. Moreover, even mild postoperative Scr elevations have been associated with long-term progression to chronic kidney disease [6,7]. Infants are particularly vulnerable to CS-AKI because of their immature renal function, limited renal reserve, and susceptibility to CPB-associated ischemia–reperfusion injury, hemolysis, oxidative stress, and systemic inflammatory responses [8–10].

Despite decades of investigation, no pharmacological intervention has consistently demonstrated efficacy in preventing CS-AKI [11,12]. Recently, intravenous amino acid (AA) therapy has emerged as a promising strategy. Previous studies have shown that continuous AA infusion significantly reduced the incidence of AKI in adults undergoing cardiac surgery with CPB [13–15], and a subsequent meta-analysis of six randomized controlled trials involving 4501 patients confirmed a reduction in the incidence of KDIGO stage 1 and stage 3 AKI [16].

Glutamine (GLN), a conditionally essential amino acid, has attracted particular interest because its circulating levels decline substantially following CPB [17,18]. Experimental studies have shown that GLN supplementation protects renal tubules through multiple mechanisms, including the induction of heat shock proteins, the attenuation of oxidative stress and inflammatory cytokine release, and the restoration of renal arginine synthesis [19–23]. In high-risk patients undergoing cardiac surgery, GLN administration significantly reduced postoperative neutrophil gelatinase-associated lipocalin (NGAL) levels [24]. However, the efficacy of GLN supplementation in the pediatric cardiac surgery population remains unknown, particularly in infants who exhibit the highest incidence of CS-AKI.

We therefore conducted a randomized, double-blind, placebo-controlled trial to determine whether perioperative intravenous GLN supplementation reduces the incidence and severity of AKI in infants and young children younger than 3 years of age undergoing elective cardiac surgery with CPB.

2. Materials and Methods

2.1. Study Design and Ethics

This was a single-center, randomized, double-blind, placebo-controlled clinical trial conducted at Shanghai Children's Hospital. This study followed the applicable CONSORT guidelines. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Shanghai Children's Hospital (approval number 2025R016-E02; date of approval: 3 March 2025) and registered at the Chinese Medical Research Registry (https://www.medicalresearch.org.cn (accessed on 15 April 2026); PID: 269707) prior to patient enrollment. Written informed consent was obtained from the parents or legal guardians of all participants. The trial was registered before patient enrollment (ChiCTR2500102350; investigator: Xiao-bing Li; registration date: 13 May 2025).

2.2. Participants

Infants and young children were eligible if they met the following inclusion criteria: (1) age under 3 years (i.e., 0–36 months); (2) scheduled for elective on-pump corrective cardiac surgery for congenital heart disease; and (3) provision of written informed consent by parents or legal guardians.

Exclusion criteria included (1) known allergy to GLN or alanyl-glutamine; (2) fever exceeding 38 °C within 24 h prior to surgery; (3) severe hepatic, renal, or cardiac dysfunction preoperatively; (4) use of aminoglycoside antibiotics or other nephrotoxic agents within 7 days prior to surgery; and (5) any condition deemed by the investigator to render the patient unsuitable for enrollment.

2.3. Randomization and Blinding

Eligible patients were randomly assigned in a 1:1 ratio to receive either intravenous GLN (GLN group) or placebo (control group). Randomization was performed using computer-generated random numbers (SPSS Statistics, version 23.0). Allocation concealment was ensured through sequentially numbered, sealed, opaque envelopes. Patients, treating clinicians, outcome assessors, and data analysts were blinded to treatment assignment throughout the study.

2.4. Study Intervention

Patients in the GLN group received intravenous alanyl-glutamine dipeptide (Ala-Gln 20% solution, 20 g/100 mL; Beijing Antu Biological Engineering Co., Ltd., Beijing, China). The study drug was initiated after induction of anesthesia and continued for 4 days (the day of surgery and the first 3 postoperative days). On the day of surgery, the dose was diluted 1:1 with 0.9% sodium chloride and infused at a rate not exceeding 0.1 g/kg/h, starting from induction of anesthesia until separation from cardiopulmonary bypass; 0.4 g/kg of the same preparation was added directly to the cardiopulmonary bypass priming solution. On each of the first 3 postoperative days, the full dose of 0.4 g/kg/day was administered by continuous intravenous infusion; the concentration and infusion rate were identical to those used for anesthetic administration on the day of surgery. The dose of 0.4 g/kg/day was selected on the basis of previous glutamine trials in cardiac surgery and established pediatric parenteral nutrition practice [17,25,26], and the 4-day course was chosen to cover the 72 h postoperative window during which the risk of AKI is highest. The detailed rationale for dose selection is discussed in the Discussion section.

2.5. Data Collection and Outcomes

The primary outcome was the incidence of AKI within 72 h after surgery, defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [27], i.e., any of the following: (1) an increase in Scr of at least 26.5 μmol/L within 48 h; (2) an increase in Scr to at least 1.5 times the baseline value, assessed within the 72 h ascertainment window; or (3) a urine output of less than 0.5 mL/kg/h persisting for 6 consecutive hours or longer. Scr was measured at baseline and at 12, 24, 48, and 72 h postoperatively; urine output was recorded hourly through an indwelling urinary catheter as part of routine postoperative care, and the oliguria criterion was applied only where at least six consecutive hours of hourly recording were available. Ascertainment therefore ended 72 h after surgery.

Secondary outcomes included (1) need for PD; (2) diuretic use; (3) Scr at baseline and 12, 24, 48, and 72 h; (4) NGAL at baseline and 12, 24, 48, and 72 h; (5) serum cystatin C (CysC) at baseline and 12, 24, 48, and 72 h; (6) procalcitonin (PCT) at baseline and 24 h; (7) ICU length of stay; (8) hospital length of stay; and (9) safety assessments including adverse events, serious adverse events, treatment interruptions, dose reduction, and discontinuations.

As shown in Table 1, safety and tolerability were assessed from the first administration of the study drug until hospital discharge. Adverse events of special interest were allergic reactions during or after infusion, abnormal liver function (elevation of alanine aminotransferase or aspartate aminotransferase to more than twice the upper limit of normal), and the need for PD. Serious adverse events included persistent renal dysfunction, defined as a serum creatinine level at least twice the preoperative baseline persisting for more than 30 days, cardiac arrest requiring cardiopulmonary resuscitation, and death. Tolerability of the study drug was evaluated by recording dose reductions, treatment interruptions, and discontinuations, which were decided solely by the treating clinicians blinded to group allocation.

Table 1. Baseline demographic and clinical characteristics.

Characteristic	Control (n = 47)	GLN (n = 47)	Standardized Difference
Age, months, median (IQR)	9.0 (1.5–12.0)	6.0 (3.0–11.0)	0.208
Male sex, n (%) [95% CI]	29 (61.7) [47.4–74.2]	23 (48.9) [35.3–62.8]	0.260
Weight, kg, median (IQR)	8.1 (4.8–9.5)	7.4 (5.8–9.6)	0.027
MAP, mmHg, median (IQR)	51.0 (45.0–54.5)	49.0 (45.0–52.0)	0.063
Preoperative HCT, %, median (IQR)	34.0 (32.0–35.0)	34.0 (32.0–35.0)	0.077
Lactate, mmol·L^{-1}, median (IQR)	0.60 (0.50–0.70)	0.50 (0.45–0.65)	0.095
PaO_2, mmHg, median (IQR)	89.0 (64.5–98.5)	69.0 (59.0–90.5)	0.323
CPB time, min, median (IQR)	68.0 (47.5–84.5)	61.0 (51.0–71.5)	0.224
ACC time, min, median (IQR)	37.0 (19.0–63.0)	34.0 (23.0–44.5)	0.236
Preoperative Scr, µmol·L^{-1}, median (IQR)	24.0 (21.0–28.0)	26.0 (22.0–30.5)	0.430
Preoperative NGAL, ng·mL^{-1}, median (IQR)	57.0 (47.0–65.0)	59.0 (50.5–64.5)	0.174
Preoperative CysC, mg·L^{-1}, median (IQR)	0.70 (0.63–0.80)	0.71 (0.65–0.76)	0.030
Preoperative PCT, ng·mL^{-1}, median (IQR)	0.030 (0.020–0.050)	0.030 (0.020–0.030)	0.259
Safety and Tolerability			
Adverse events, n (%)	6 (12.8)	0 (0.0)	—
Allergic reaction, n	0	0	—
Abnormal liver function, n	0	0	—
Peritoneal dialysis, n	6	0	—
Serious adverse events, n	0	0	—
Persistent renal dysfunction, n	0	0	—
Cardiopulmonary resuscitation, n	0	0	—
Death, n	0	0	—
Dose reduction, n	0	0	—
Treatment interruption, n	0	0	—
Discontinuation, n	0	0	—

MAP, mean arterial pressure; HCT, hematocrit; PaO_2, arterial partial pressure of oxygen; CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; Scr, serum creatinine; NGAL, neutrophil gelatinase-associated lipocalin; CysC, cystatin C; PCT, procalcitonin. Standardized differences were interpreted as follows: <0.1 negligible, 0.1–0.2 small, 0.2–0.5 moderate, and >0.5 large. p values were not adjusted for multiplicity. Moderate imbalances were present for PaO_2, ACC time, preoperative Scr, male sex, CPB time, age, and PCT. Persistent renal dysfunction was defined as a serum creatinine level at least twice the preoperative baseline persisting for more than 30 days.

Clinical data were collected prospectively, including age, sex, weight, baseline mean arterial pressure (MAP) measured invasively before the induction of anesthesia, preoperative hematocrit (HCT), lactate, arterial partial pressure of oxygen (PaO_2), CPB duration, and aortic cross-clamp (ACC) time. The surgical procedure performed, the congenital cardiac diagnosis, and the RACHS-1 (Risk Adjustment in Congenital Heart Surgery) category were also recorded. Blood samples were collected at predefined time points for measurement of Scr, serum NGAL, serum CysC, and serum PCT. All samples were processed and tested following clinical laboratory standards and the manufacturer's instructions. Laboratory personnel remained blinded to the treatment allocation throughout sample processing and testing.

2.6. Statistical Analysis

All analyses were conducted according to the intention-to-treat principle, with all patients retained in their assigned groups. No patients were excluded from these analyses after randomization.

Continuous variables are presented as median with interquartile range (IQR), and categorical variables as count (percentage) with 95% confidence interval (CI). Baseline characteristics were compared using standardized differences, interpreted according to the conventional thresholds: <0.1 negligible, 0.1–0.2 small, 0.2–0.5 moderate, and >0.5 large. For between-group comparisons of continuous variables, the Mann–Whitney U test was used. Categorical outcomes were compared using the two-sided Fisher's exact test.

Changes in biomarkers from baseline (Δ values) were calculated as postoperative minus preoperative values.

Effect sizes for binary outcomes were expressed as relative risk (RR) with 95% CI, and absolute risk differences were also computed (Newcombe method). As the study was an initial, exploratory investigation, no adjustments were made for multiple comparisons. This approach was based on the following considerations. First, the trial had a single pre-specified primary endpoint: the incidence of AKI within 72 h, and the confirmatory inference of the study rests solely on this endpoint. Second, the secondary clinical endpoints and biomarker comparisons were considered exploratory. Third, in a trial of this size, multiplicity adjustment would substantially reduce statistical power and may obscure clinically meaningful signals that warrant confirmation in larger studies. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS (version 23.0).

The primary outcome was further analyzed using multivariable logistic regression. Three sequential models were constructed: Model 1 included age, sex, and weight; Model 2 additionally included preoperative Scr, CPB time, and arterial PaO_2; and Model 3 included preoperative Scr, CPB time, and ACC time and was restricted to the patients with complete data (Supplemental Table S1). Results are reported as adjusted odds ratios (OR) with 95% CI.

The sample size was calculated based on the incidence of AKI. In accordance with a previous report, the incidence of AKI, which was the primary outcome, was estimated at 38.7% in the control group according to KDIGO [28]. On the basis of data from the results of Kazawa et al. [29], the absolute risk reduction associated with amino acid administration was estimated as 26%, corresponding to an expected AKI incidence of 12.7% in the GLN group. With this information, we performed a two-sided test with an α level of 0.05 and 80% power, and the calculated sample size was 42 patients per group. To account for an anticipated dropout rate of 10%, the target enrollment was increased to 47 patients per group, resulting in a total planned sample size of 94 patients.

3. Results

3.1. Patient Characteristics

A total of 94 infants and young children were enrolled and randomly assigned to the GLN group ($n = 47$) or the control group ($n = 47$). All patients completed the study and were included in the final analysis; all 94 randomized patients were analyzed in the group to which they were assigned, with no crossovers, no dropouts, and no losses to follow-up (Figure 1). The schedule of randomization, alanyl-glutamine or saline administration, sample collection, and primary and secondary outcome assessments is summarized in Figure 2. Baseline demographic and clinical characteristics, as well as perioperative characteristics are shown in Table 1. No variable showed a large imbalance between groups (all standardized differences < 0.5). Moderate imbalances were observed for PaO_2 (0.323), ACC time (0.236), preoperative Scr (0.430), male sex (0.260), PCT (0.259), CPB time (0.224), and age (0.208) (Table 1). The median age was 9.0 months (IQR, 1.5–12.0) in the control group and 6.0 months (IQR, 3.0–11.0) in the GLN group; overall, 78.7% of patients were aged ≤12 months, and the age range was 1–36 months. Males accounted for 61.7% and 48.9% of participants in the control and GLN groups, respectively. The median CPB duration was 68.0 min (IQR, 47.5–84.5) in the control group and 61.0 min (IQR, 51.0–71.5) in the GLN group. Preoperative NGAL and CysC levels were similar between the two groups.

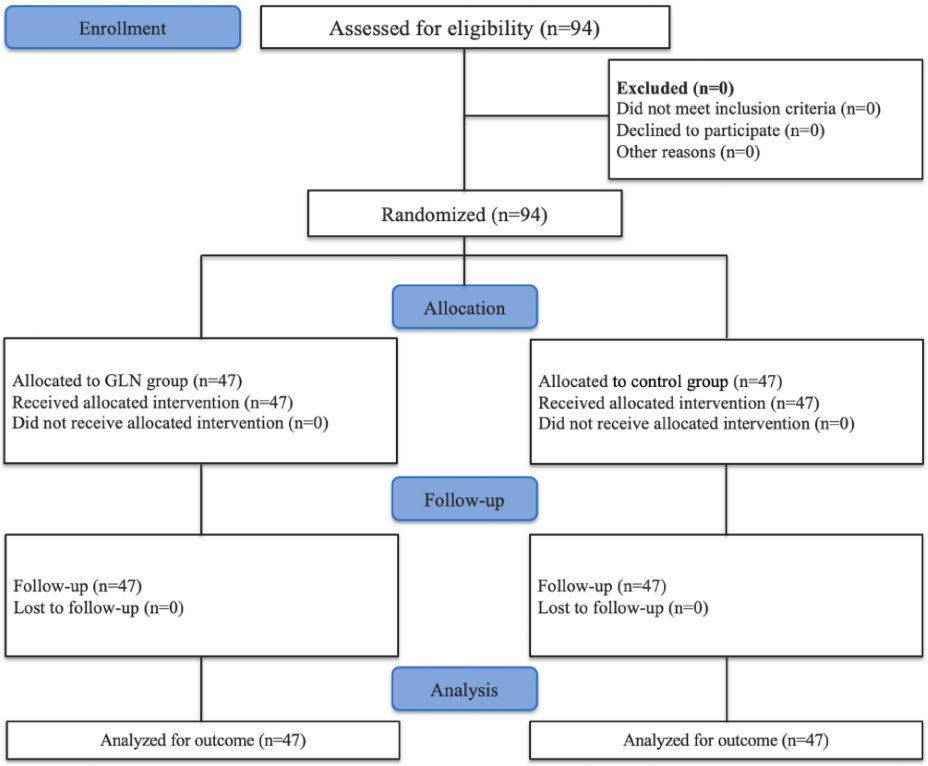


Figure 1. CONSORT participant flow diagram. Of the 94 randomized patients, 47 were allocated to the glutamine group and 47 to the control group; all 94 were analyzed, with no dropouts, withdrawals, or losses to follow-up. CONSORT, Consolidated Standards of Reporting Trials.

The congenital cardiac diagnoses and the surgical procedures performed are summarized in Table S2. Ventricular septal defect (44.7% vs. 57.4%) and atrial septal defect or patent foramen ovale (85.1% vs. 74.5%) were the most common lesions in both control and GLN groups, respectively. Surgical complexity, classified by the RACHS-1 category, did not differ significantly between groups (Category 1: 7 vs. 4; Category 2: 7 vs. 15; Category 3: 30 vs. 26; Category 4: 3 vs. 2; $p = 0.39$ for the comparison of Categories 1–2 versus 3–4).

3.2. Primary and Key Clinical Outcomes

The incidence of AKI, defined according to KDIGO criteria, was 40.4% (95% CI, 27.6–54.7) in the control group compared with 14.9% (95% CI, 7.4–27.7) in the GLN group ($p = 0.010$; RR, 0.37) (Table 2). Among the 19 control patients meeting the primary endpoint, 14 satisfied the Scr criteria, and 5 satisfied the urine output criterion. In the GLN group, all 7 patients meeting the endpoint satisfied the Scr criteria, as shown in Table S3.

The proportion of patients who developed severe AKI (KDIGO stages 2–3) was lower in the GLN group than in the control group (8.5% vs. 14.9%), although the difference did not reach statistical significance ($p = 0.523$; RR, 0.57). Notably, all patients with KDIGO stage 3 AKI in the control group required PD, whereas all patients with KDIGO stage 3 AKI in the GLN group met the stage 3 criteria solely on the basis of Scr levels and did not require PD.

In multivariable logistic regression analyses adjusting for baseline imbalances (Supplemental Table S1), the association between GLN and AKI remained significant: age, sex, and weight (adjusted OR 0.25, 95% CI 0.09–0.72; $p = 0.010$); plus preoperative creatinine, CPB time, and PaO_2 (OR 0.30, 95% CI 0.10–0.95; $p = 0.040$); and preoperative creatinine, CPB time, and ACC time (OR 0.30, 95% CI 0.10–0.89; $p = 0.030$).

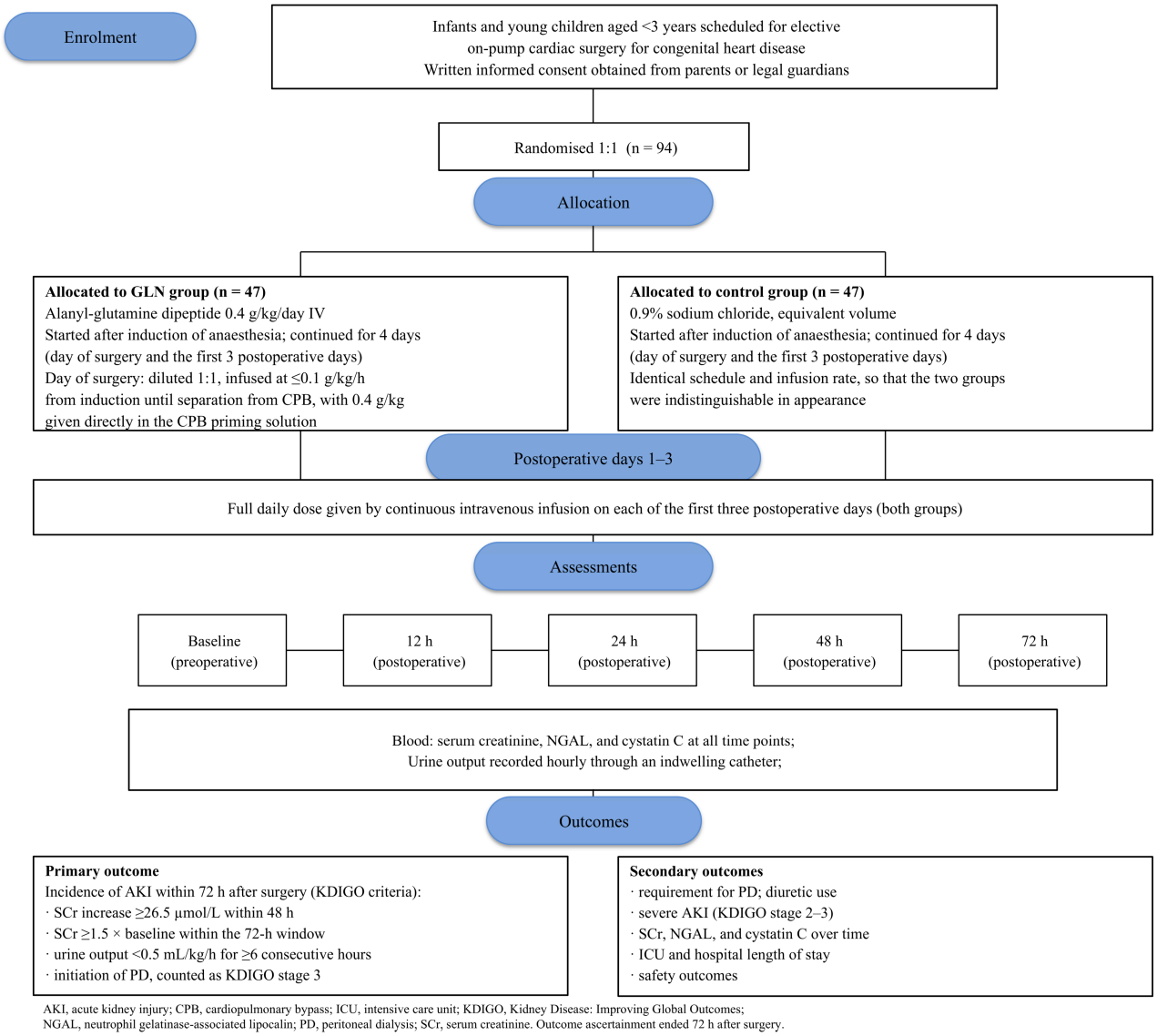


Figure 2. Study design and assessment schedule. AKI, acute kidney injury; CPB, cardiopulmonary bypass; NGAL, neutrophil gelatinase-associated lipocalin.

Table 2. Primary and key clinical outcomes.

Outcome	Control (n = 47)	GLN (n = 47)	p-Value	RR (95% CI)
AKI within 72 h, n (%) [95% CI]	19 (40.4) [27.6–54.7]	7 (14.9) [7.4–27.7]	0.010 *	0.37 (0.17–0.82)
Severe AKI (Stage 2–3), n (%) [95% CI]	7 (14.9) [7.4–27.7]	4 (8.5) [3.4–19.9]	0.523	0.57 (0.18–1.82)

RR, relative risk (GLN group vs. control group; RR < 1 favors GLN); CI, confidence interval; Scr, serum creatinine. * $p < 0.05$. AKI was adjudicated using creatinine and urine output; initiation of renal replacement therapy (PD) was counted as stage 3 AKI. Risk differences (GLN minus control): AKI −25.5% (95% CI −43.6% to −9.5%). RR was calculated using the Katz log method. p values were not adjusted for multiplicity.

3.3. Secondary Clinical Outcomes

The requirement for PD was lower in the GLN group than in the control group (0.0% vs. 12.8%; $p = 0.026$; risk difference, −12.8% [95% CI, −22.9% to −0.4%]). Diuretic use was also less frequent in the GLN group than in the control group (6.4% vs. 23.4%; $p = 0.040$) (Table 3).

Table 3. Secondary clinical outcomes.

Outcome	Control (n = 47)	GLN (n = 47)	p-Value	RR (95% CI)
PD, n (%) [95% CI]	6 (12.8) [6.0–25.2]	0 (0.0) [0.0–7.6]	0.026 *	0.08 (0.00–1.33) †
Diuretics use, n (%) [95% CI]	11 (23.4) [13.6–37.2]	3 (6.4) [2.2–17.2]	0.040 *	0.27 (0.08–0.92)
ICU stay, h, median (IQR)	75.0 (45.0–140.5)	72.0 (46.5–169.0)	0.408	—
Hospital stay, d, median (IQR)	16.0 (10.0–21.0)	14.0 (10.2–21.5)	0.694	—

PD, peritoneal dialysis; ICU, intensive care unit; RR, relative risk (GLN vs. control); CI, confidence interval; IQR, interquartile. † Haldane correction (+0.5) applied for zero-cell calculation. * $p < 0.05$. Risk differences (GLN minus control): PD −12.8% (95% CI, −22.9% to −0.4%). p values were not adjusted for multiplicity.

NGAL levels were significantly lower in the GLN group than in the control group at 24, 48, and 72 h postoperatively (Figure 3A). At 24 h, median NGAL was 93.0 ng/mL (IQR, 67.0–126.0) in the control group and 68.0 ng/mL (IQR, 53.6–88.5) in the GLN group ($p < 0.001$). Similar differences were observed at 48 h (85.0 vs. 59.0 ng/mL; $p = 0.003$) and 72 h (69.0 vs. 68.0 ng/mL; $p = 0.032$). Meanwhile, ΔNGAL values were also lower in the GLN group at 24, 48, and 72 h (all $p < 0.05$) (Figure 3C).

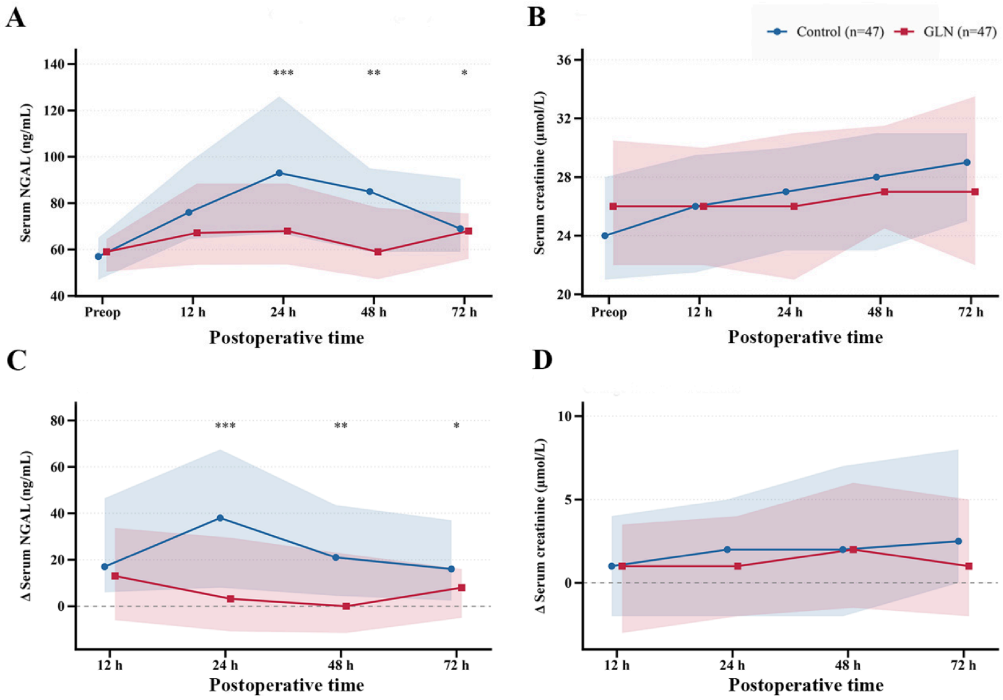


Figure 3. Postoperative time course of serum NGAL (**A**), serum creatinine (**B**), Δ serum NGAL (**C**), and Δ serum creatinine (**D**) in the GLN and control groups. Points and lines represent medians, and shaded bands indicate the IQR at each assessment time point (preoperative, 12, 24, 48, and 72 h). Pairwise comparisons were performed by the Mann–Whitney U test; p values were not adjusted for multiplicity. Δ = postoperative–preoperative. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. NGAL, neutrophil gelatinase-associated lipocalin.

In contrast, perioperative Scr levels were compared between the two groups throughout the study period (Figure 3B). Median preoperative Scr was 24.0 μmol/L (IQR, 21.0–28.0) in the control group and 26.0 μmol/L (IQR, 22.0–30.5) in the GLN group ($p = 0.108$). At 72 h postoperatively, median Scr was 29.0 μmol/L (IQR, 25.0–31.0) and 27.0 μmol/L (IQR, 22.0–33.5) in the control and GLN groups ($p = 0.620$). No statistically significant differences were observed in ΔScr at any postoperative time point (Figure 3D).

No significant differences between these two groups were observed in serum CysC levels and PCT values at any assessed time point (all $p > 0.05$; Supplemental Tables S4 and S5). The median duration of ICU stay was 75.0 h (IQR, 45.0–140.5) in the control group and 72.0 h (IQR, 46.5–169.0) in the GLN group ($p = 0.408$). Median hospital stay was 16.0 days (IQR, 10.0–21.0) and 14.0 days (IQR, 10.2–21.5) ($p = 0.694$) (Table 3).

No adverse events, serious adverse events, or treatment modifications related to the study drug occurred in either group (Table 1). The only adverse event recorded was the need for PD in six control patients (6/47, 12.8%), which reflected the management of postoperative AKI rather than drug toxicity.

4. Discussion

This randomized, double-blind, placebo-controlled trial shows that perioperative intravenous GLN supplementation was associated with a lower incidence of AKI, a reduced requirement for PD, and less frequent use of diuretics in infants and young children undergoing elective cardiac surgery with CPB. Moreover, GLN-treated patients showed consistently lower postoperative NGAL concentrations, indicating attenuated early renal tubular injury. To our knowledge, randomized controlled trials evaluating perioperative glutamine supplementation for the prevention of cardiac surgery-associated AKI in infants are rare [29].

Our findings align with and extend previous studies that evaluated the renoprotection of amino acid supplementation during the perioperative period of cardiac surgery in infants. Previous studies have shown that a single preoperative amino acid infusion shortened the duration of AKI in adults [13], and a multicenter trial demonstrated a reduction in AKI incidence [14]. A meta-analysis further reported that amino acid-based interventions significantly reduced the incidence of KDIGO stage 1 and stage 3 AKI [16]. In our study, although glutamine supplementation reduced the overall incidence of AKI, no statistically significant difference was observed in the incidence of severe AKI (KDIGO stages 2–3). As the sample size was calculated for the overall incidence of AKI, this subgroup analysis was not prespecified in the study protocol, and the trial was powered only for the primary outcome; the severe-AKI comparison is therefore exploratory and possibly underpowered. The effect on severe AKI remains uncertain and requires further evaluation in larger trials. Intravenous glutamine at 0.4 g/kg/day has been shown to reduce biomarkers of renal injury in adults undergoing cardiac surgery [25], and perioperative alanyl-glutamine at 0.5 g/kg/day for 3 days has been evaluated in adult cardiac surgical patients [26], whereas in pediatric parenteral nutrition practice glutamine dipeptide is typically provided at 0.3–0.5 g/kg/day [17]. We therefore selected a dose of 0.4 g/kg/day, initiated at the induction of anesthesia to ensure substrate availability before CPB-induced injury occurs, and continued treatment for 4 days to cover the entire 72-h window of highest AKI risk. Whether this dose is optimal for infants—whose glutamine metabolism, glutathione kinetics, and volume of distribution differ substantially from those of adults—remains uncertain; the intermediate-dose efficacy observed here (14.9% vs. 40.4% AKI incidence) supports further dose-finding studies in this population.

Several studies have suggested a potential benefit of GLN in adult cardiac surgery. In high-risk adults, GLN reduced postoperative NGAL levels, although this was not accompanied by a significant reduction in overall AKI incidence [24]. In patients undergoing mitral valve replacement, preoperative GLN was also associated with lower NT-proBNP levels and shorter ICU and hospital stays [25]. However, other studies found little effect on inflammatory markers [26] or renal function [30]. Differences in patient selection and baseline risk may partly account for these inconsistent findings [31]. The apparent discrepancy with the trial by Weiss et al. [24], which reported lower NGAL concentrations

in the absence of a reduction in clinical AKI in adults, may be explained by several differences. First, the populations differ fundamentally: Weiss et al. studied high-risk adults after cardiac surgery, whereas our cohort consisted of infants and young children with immature renal function and limited renal reserve, in whom injury related to CPB may be more responsive to substrate supplementation. Second, the timing and dose differed: our patients received 0.4 g/kg/day for 4 days beginning at induction, including a CPB-priming dose, whereas the adult trial gave glutamine only after surgery. Third, the endpoints differed: the primary endpoint of the adult trial was a biomarker of tubular injury, and that study was not powered to detect a difference in clinical AKI. Fourth, the baseline risk differed substantially, with a 40.4% AKI incidence in our control group compared with 25% in the adult study. Importantly, GLN supplementation was associated with a lower incidence of AKI, and no GLN-treated infants required PD. These more favorable clinical outcomes may be attributable to differences in both the study population and the intervention strategy. Infants possess immature renal function and limited renal reserve, rendering them particularly susceptible to CPB-induced injury while potentially more responsive to preventive interventions. Furthermore, our GLN dosing regimen (0.4 g/kg/day for 4 days, including intraoperative CPB priming) achieved earlier and more sustained drug exposure. These findings are supported by previous experimental studies demonstrating that early glutamine administration enhances heat shock protein expression and suppresses inflammatory signaling before irreversible tubular injury develops [20,32,33].

The biological plausibility of glutamine-mediated renoprotection is supported by multiple experimental studies. Glutamine serves as a major metabolic substrate for renal tubular epithelial cells, supporting mitochondrial ATP production and cellular energy homeostasis [34]. In addition, glutamine contributes to de novo arginine synthesis via the glutamine–citrulline–arginine pathway [19,35]. Furthermore, previous studies have demonstrated that GLN reduces tubular injury primarily through immunomodulation, enhancement of HSP70 expression, and suppression of NF-κB-mediated inflammatory signaling [20–22,36]. Clinical evidence also indicates that perioperative glutamine supplementation restores impaired renal arginine synthesis following open abdominal aortic surgery, providing further mechanistic support for its renoprotective effects [35].

We also observed a reduction in the requirement for PD, indicating the potential clinical relevance of perioperative glutamine supplementation. PD remains the predominant form of renal replacement therapy in pediatric patients undergoing cardiac surgery and is typically reserved for patients with severe AKI accompanied by fluid overload or refractory metabolic disturbances. Its use is strongly associated with prolonged ICU stays and adverse outcomes [37]. Our findings raise the possibility that GLN may attenuate AKI severity. PD was required less frequently in the GLN group; however, this secondary finding should be interpreted cautiously because of the small number of events. This is corroborated by the pronounced reduction in NGAL levels observed in the GLN group at 24, 48, and 72 h postoperatively, consistent with GLN-mediated attenuation of ongoing tubular stress during the vulnerable postoperative period [38,39]. Previous studies have shown that elevations in tubular injury biomarkers are associated with adverse outcomes, even in the absence of creatinine-defined AKI [40–42]. Thus, the reduction in NGAL levels in the GLN group may confer prognostic benefit beyond the reduction in overt AKI. Therefore, the persistent suppression of NGAL in the GLN group suggests the attenuation of subclinical tubular injury that may not be reflected by conventional Scr measurements. Furthermore, the reduced requirement for diuretics may reflect better preservation of renal function and postoperative fluid homeostasis. Collectively, these observations suggest that perioperative GLN supplementation may be associated with a lower incidence of postoperative AKI and lower levels of early renal tubular injury biomarkers in infants undergoing elective

cardiac surgery. The biomarker findings may reflect differences in renal injury not fully captured by conventional Scr-based assessment. Perioperative glutamine supplementation showed promising results in reducing postoperative AKI incidence in infants undergoing elective cardiac surgery. However, these findings are exploratory and require confirmation in multicenter randomized controlled trials before this intervention can be recommended for routine clinical practice.

Perioperative alanyl-glutamine supplementation was well tolerated in this cohort. No allergic reactions or hepatic abnormalities were observed, and no serious adverse events (persistent renal dysfunction, cardiac arrest requiring resuscitation, or death) occurred in either group. All patients completed the full 4-day course without dose reduction, interruption, or discontinuation, indicating that 0.4 g/kg/day is feasible even in small infants. These findings are consistent with the safety record of intravenous glutamine in previous randomized trials of adult cardiac surgery [24–26]. Nevertheless, patients with shock, severe hepatic dysfunction, or preexisting renal failure were excluded from our trial, and the safety and efficacy of glutamine in these higher-risk populations remain to be established.

Although no differences were observed in ICU or hospital length of stay, GLN use may reduce hospitalization costs because of the lower requirement for PD and less diuretic use. The cost of GLN was approximately CNY 40 (≈US $5.6) per child for the entire course. This low supplementation cost, together with reduced resource use, suggests potential cost savings. However, formal cost-effectiveness analyses incorporating total treatment costs and clinical outcomes are needed in larger, multicenter cohorts.

However, our study has several limitations. This single-center trial with a modest sample size may limit the generalizability of the findings. No long-term outcomes were collected, so delayed AKI and later kidney outcomes could not be assessed. Plasma glutamine concentrations were not recorded. Therefore, biological exposure could not be verified. Postoperative weight changes and fluid balance were not recorded, which may dilute Scr and interfere with the diagnosis of AKI. The optimal dose, duration, and timing of glutamine administration remain undefined, and, despite consistent results across adjusted models, residual confounding cannot be excluded. Multicenter trials with pharmacokinetic monitoring, prespecified endpoints, and extended renal follow-up are therefore required.

5. Conclusions

In this single-center trial of infants and young children undergoing elective cardiac surgery with CPB, perioperative intravenous GLN supplementation was associated with a lower incidence of AKI, a lower requirement for PD, and less frequent diuretic use, together with consistently lower postoperative NGAL concentrations, suggesting attenuated early tubular injury. Collectively, these exploratory findings suggest that GLN may be a promising perioperative renoprotective strategy for this particularly vulnerable population, and warrant confirmation in larger multicenter trials to establish its efficacy, optimal dosing, and long-term clinical benefits.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/nu18223859/s1, Table S1: Multivariable Logistic Regression Analyses of the Primary Outcome. Table S2: Congenital Cardiac Diagnoses, Surgical Complexity, and Procedures. Table S3: Components of the Composite KDIGO Primary Endpoint. Table S4: Serum Cystatin C Levels (mg/L). Table S5: Procalcitonin Levels (ng/mL).

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Institutional Review Board Statement: The study protocol was approved by the Institutional Review Board of Shanghai Children's Hospital (2025R016-E02, 3 March 2025) and registered at the Chinese Clinical Trial Registry (https://www.chictr.org.cn/; ChiCTR2500102350; investigator: Xiao-bing Li; registration date: 13 May 2025) prior to patient enrollment. Written informed consent was obtained from the parents or legal guardians of all participants.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

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