Intravenous amino acid therapy for kidney protection in cardiac surgery patients: A pilot randomized controlled trial

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ABSTRACT

Objective: To determine whether a continuous intravenous infusion of standard amino acids could preserve kidney function after on-pump cardiac surgery.

Methods: Adult patients scheduled to receive cardiac surgery lasting longer than 1 hour on-pump were randomized to standard care ($n = 36$) or an infusion of amino acids initiated immediately after induction of anesthesia ($n = 33$). The study's primary outcome measurements assessed renal function. These assessments included duration of renal dysfunction, duration and severity of acute kidney injury (AKI), estimated glomerular filtration rate (eGFR) over time, urine output, and use of renal-replacement therapy. Complications and other measures of morbidity were also assessed.

Results: Sixty-nine patients (mean age 71.5 [standard deviation 9.2] years; 19 of 69 women) were enrolled and randomized. Patients received coronary artery bypass graft surgery (37/69), valve surgery (24/69), coronary artery bypass graft and valve surgery (6/69), or other procedures (2/69). Mean on-pump time was 268 [standard deviation 136] minutes. Duration of renal dysfunction did not differ between the groups (relative risk, 0.86; 95% confidence interval [CI], 0.19-3.79, $P = .84$). However, patients who received the amino acid infusion had a reduced duration of AKI (relative risk, 0.02; 95% CI, 0.005-0.11, $P < .0001$) and greater eGFR (+10.8%; 95% CI, 1.0%-20.8%, $P = .033$). Daily mean urine output was also significantly greater in patients who received the amino acid infusion (1.4 ± 0.5 vs 1.7 ± 0.9 L/d; $P = .046$).

Conclusions: Commencing an infusion of standard amino acids immediately after the induction of anesthesia did not alter duration of renal dysfunction; however, other key measures of renal function (duration of AKI, eGFR and urine output) were significantly improved. These results warrant replication in multicenter clinical trials. (J Thorac Cardiovasc Surg 2019;157:2356-66)

Estimated glomerular filtration rate by study day for patients randomly allocated to receive a continuous infusion of amino acids or standard care: percent change from presurgery baseline.

Central Message

Cardiac surgery-associated acute kidney injury may be prevented by commencing an intravenous infusion of standard amino acids immediately after induction of anesthesia.

Perspective

Cardiopulmonary bypass impairs renal oxygenation by inducing an increase in renal vascular resistance that results in reduced renal blood flow, even when cardiac index is increased. After healthy adults eat a high-protein meal, afferent arteriolar vasodilatation occurs, which increases renal blood flow. Protein intake initiated during bypass surgery may ameliorate the onset of acute kidney injury.

See Commentary on page 2367.

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Abbreviations and Acronyms

AKI	= acute kidney injury
CI	= confidence interval
CONSORT	= Consolidated Standards of Reporting Trials
CPB	= cardiopulmonary bypass
eGFR	= estimated glomerular filtration rate
GFR	= glomerular filtration rate
HDU	= high-dependency unit
ICU	= intensive care unit
RCT	= randomized controlled trial
RRT	= renal-replacement therapy
SD	= standard deviation

Scanning this QR code will take you to the article title page to access supplementary information.

Acute kidney injury (AKI) has become one of the most common complications after cardiac surgery, with up to 40% of all patients developing AKI at some time during their recovery.¹ While the onset of AKI after cardiac surgery is associated with a 10-fold increase in mortality, caring for patients with cardiac surgery-associated AKI increases hospital costs to the US health care system by \$1.01 billion per year.² Despite these huge health and cost implications, there are no reliable means to treat cardiac surgery-associated AKI.³

On-pump cardiac surgery presents significant challenges to the maintenance of normal renal function. Exposure to cardiopulmonary bypass (CPB) impairs renal oxygenation by inducing an increase in renal vascular resistance that results in a redistribution of blood flow away from the kidney, even when cardiac index is increased.⁴ In addition, hypothermia, hemodilution, hypotension, hemolysis, and low-flow cardiac output states all have direct and independent effects that reduce renal blood flow by increasing renal vascular resistance.³ Ischemic and inflammatory stress arising from reduced renal blood flow have been proposed as major contributors toward the onset of cardiac surgery-associated AKI.⁵

Eating a high-protein meal is known to have a major influence on renal hemodynamics. High-protein intake results in afferent arteriolar vasodilatation and a decrease in renal vascular resistance with a consequent increase in renal blood flow.^{6,7} In response, glomerular filtration rate (GFR) increases by up to 35% over resting baseline GFR.^{8,9}

The kidney's normal hyperemic response to protein intake can be viewed teleologically as a mechanism developed to enhance the elimination of nitrogenous wastes arising from a protein meal.⁷ This response to protein intake is conserved across many species of mammals,^{7,10} and multiple local and systemic mechanisms have been proposed as modulators.¹¹ Although it is accepted that protein intake alters single-nephron GFR via the tubuloglomerular feedback mechanism, protein intake alters overall renal vascular resistance through local receptors (N-methyl-D-aspartate glutamate receptor) and humoral factors (nitric oxide, insulin, glucagon, prostaglandins, etc).¹² Understanding of the necessary and sufficient interactions between each specific mechanism is evolving but remains incomplete.^{11,12}

A randomized controlled trial (RCT) conducted in 22 adult patients undergoing cardiac surgery demonstrated that an infusion of amino acids commenced immediately after surgery can significantly increase renal blood flow, GFR, and renal oxygen consumption in this patient population.¹³ Animal models show that the resultant increase in renal blood flow after a protein meal can protect the kidney from acute ischemic insults.¹⁰ We hypothesized that an infusion of amino acids, commenced before exposure to CPB, may help maintain renal blood flow, thus ameliorating the ischemic and inflammatory injury that contributes toward the onset of cardiac surgery-associated AKI. We conducted this pilot parallel RCT to test this hypothesis. Patients were randomly allocated to standard care or to commence an infusion of amino acids after induction of anesthesia.

METHODS

This single-center study was conducted at the Royal North Shore Hospital, Sydney, Australia. Approval was obtained from the participating site's Human Research Ethics Committee (April 17, 2012: Reference Number 1201-024M, HREC/12/HSWKE/28). The trial is registered in the Australian and New Zealand Clinical Trials Registry (anzctr.org.au ACTRN12612000134820). Patients provided written informed consent before enrollment in accordance with local and national laws. Conduct and reporting are consistent with the 2010 Consolidated Standards of Reporting Trials (CONSORT) extension for pilot trials (Figure E1 and Online Data Supplement 1).¹⁴

Adult patients who were scheduled to undergo cardiac surgery expected to require longer than 1 hour on-pump were considered eligible. Only patients with current estimated glomerular filtration rate (eGFR) less than 90 mL/min/1.73 m² were enrolled, as patients with pre-existing renal compromise are more likely to develop subsequent AKI, thus improving the power of this small pilot project.³ If the patient's eGFR was less than 20 mL/min/1.73 m², they were not eligible for recruitment. See Online Data Supplements 2 and 3 for complete eligibility criteria.

Allocation concealment was maintained by use of a central randomization web server. eGFR was considered a potentially important baseline prognostic variable. To prevent extreme imbalance, 2 strata were defined by eGFR at time of randomization based on whether eGFR was greater than or less than 30 mL/min/1.73 m² and the randomization was conducted separately within each stratum. The sequence was generated to achieve a 1:1 allocation ratio using blocks of variable size with random seeds.¹⁵

Investigators were required to attend a small-group start-up meeting and complete a formal study run-in phase to become familiar with the application of eligibility criteria and use of the dosing algorithm before recruiting their first patient.¹⁶

Interventions

If randomized to the intervention arm, the patient received a continuous infusion of a standard mixture of L-amino acids (Synthamin 17 Electrolyte Free; Baxter Healthcare, Sydney, Australia) delivered at a rate of 42 mL/h to achieve a daily protein intake of at least 100 g/day. This dose of intravenous amino acids has previously been shown to result in a significant and marked increase in GFR in healthy elderly adults.⁸ The infusion was begun after anesthetic induction and was administered through a dedicated central line and commenced at the time the central line was placed. The infusion continued until the patient was discharged from the intensive care unit (ICU)/high-dependency unit (HDU) to the ward.

If the patient commenced any form of nutritional support while in the ICU/HDU, the infusion rate of the study L-amino acid intervention was reduced such that the total protein intake from all sources (nutrition and study intervention) was 2.0 g/kg/day. The study intervention was not blinded. Complete details of the dosing algorithm are provided in [Online Data Supplement 2](#).

Standard care was defined pragmatically. In both the study intervention and the standard care group, the attending clinician determined all aspects of intraoperative and postoperative care, including anesthetic regimen, CPB parameters, fluid replacement, and nutrition support based on their standard practice and individual patient's needs, independent of the study intervention. Additional information regarding intraoperative care is presented in [Online Data Supplement 2](#).

Primary Outcomes: Measures of Renal Function

The primary measure of renal function was defined a priori as the duration of renal dysfunction after surgery using the validated threshold for clinically significant renal dysfunction determined by the Brussels Table (creatinine >168 $\mu\text{mol/L}$),¹⁷ which is equivalent to a Sepsis-related Organ Failure Assessment renal domain score greater than 1.¹⁸ Efficacy was also assessed by analyzing the duration of AKI after surgery, defined and staged using the Kidney Disease: Improving Global Outcomes criteria.¹⁹ Duration was defined as the total number of days after onset whereby the worst (greatest) creatinine value available during each calendar day on study met the prespecified criteria for renal dysfunction or AKI.

Additional measures of renal function included eGFR calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation, developed by Levey and colleagues²⁰; eGFR, calculated from serum cystatin C using the equations developed by Stevens and colleagues²¹; and use of renal-replacement therapy (RRT).

Secondary Outcomes: Measures of Morbidity

Secondary outcomes included measures of intraoperative and postoperative care (duration of surgery, crossclamp time, ICU stay, hospital stay, mechanical ventilation days, etc) and patient-centered outcomes (vital status at study day 90; Zubrod/World Health Organization Performance Status²²; RAND-36 General Health Status Ver 1; RAND-36 Physical Function scale Ver 1).²³

Creatinine and Cystatin C Assays

Creatinine was assayed using the Abbott Architect Jaffe method. The assay has a coefficient of variation of 2.1% at 70 $\mu\text{mol/L}$ and 1.7% at 510 $\mu\text{mol/L}$. Samples for creatinine assay were routinely collected on each day of ICU/HDU and hospital admission.

Serum cystatin C was assayed using the particle-enhanced turbidimetric immunoassay on the Abbott Architect c4000 chemistry analyzer (Abbott,

Abbott Park, Ill). The cystatin C assay has a coefficient of variation of 3.5% at 0.34 mg/L, 3.6% at 0.58 mg/L, 2.7% at 0.88 mg/L, and 3.6% at 4.2 mg/L. To reduce sample collection, handling, and processing costs, a skip pattern was used to optimize information gain: samples for cystatin C assay were obtained every second day for the first week and every third day thereafter, up to study day 16.

Sample Size, Power, and Statistical Analysis

Sample size estimation calculated 72 patients would be required to provide 80% power to detect a reduction in duration of renal dysfunction between groups of 2.2 days, assuming a variance of 11 days. Estimates of the potential treatment effect and variance were obtained from previously collected data demonstrating a reduction in duration of renal dysfunction in general critically ill patients attributable to improved protein intake²⁴ and are based on data from the subset of cardiac surgery patients enrolled in this larger trial, which also showed significant benefit.

Analysis of the effect of treatment on the primary outcome and other count data (hospital stay, ICU/HDU stay, duration of ventilation, duration of RRT, etc) was conducted using Poisson regression adjusted for time at risk (hospital stay) using an offset term where appropriate. When an offset term was employed, outcomes are presented as count per 10 hospital days. If the scaled deviance exceeded 1.4 units per degree of freedom, a conservative negative-binomial model was employed. A prespecified algorithm was used to identify baseline characteristics for inclusion in a covariate adjusted regression model to control for confounding.²⁵

Repeated measures over time, such as eGFR or urea, were assessed using a nested analysis of variance, controlling for baseline values of the repeated measure. Dichotomous outcomes were assessed using an exact Pearson χ^2 test, with unconditional exact 95% confidence intervals (CI) calculated around the risk difference. Under the Central Limit Theorem, given that samples of continuous biological variables arise from populations with finite means and finite variances, continuous biological variables were analyzed using *t*-tests and presented as mean and standard deviation (SD).

All analysis was conducted under the principle of intention to treat. All analytic decision thresholds were declared a priori in a previously published statistical analysis plan.²⁵ A 2-sided *P*-value less than .05 was accepted to indicate statistical significance. Analysis was conducted in SAS version, 9.2 (SAS Institute, Cary, NC).

RESULTS

From March 5, 2013, to April 26, 2016, 73 adult patients scheduled to undergo elective or urgent on-pump cardiothoracic surgery at the Royal North Shore Hospital, Sydney, Australia, provided consent to participate. Two consented patients became ineligible before surgery (1 surgery cancelled and 1 fluid intake restricted to less than 1 L per day) and were not randomized. Of the 71 patients who were randomized before surgery, 2 were rescheduled to receive surgery off-pump and were therefore not eligible for enrollment. [Figure 1](#) presents a CONSORT patient flow diagram.

Baseline Balance

The mean age of enrolled patients was 71.5 years, with an SD of 9.2 years. Fifty-four percent (37/69) of enrolled patients had coronary artery bypass graft surgery only, 34.7% (24/69) had valve surgery only, 8.7% (6/69) had coronary artery bypass graft plus valve surgery, and 2.9% (2/69) had other procedures. Sixteen percent (11/69) of

FIGURE 1. The Consolidated Standards of Reporting Trials 2010 Patient Recruitment Flow Diagram. Number of patients consented, randomly allocated, followed up, and analyzed.

patients had previous cardiac surgery. By chance, significantly more female patients (5/36 vs 14/33, $P = .01$) were randomly allocated to the study intervention group. No other baseline characteristics exhibited significant imbalance. Additional demographics and patient characteristics are presented in [Table 1](#).

Study Process Measures

One hundred percent (33/33) of enrolled patients allocated to the study intervention group received supplementary amino acids during their on-pump procedure. During surgery, the mean duration of the 42 mL/h infusion was 318 (SD 99) minutes, resulting in the delivery of 223 (SD 69) mL of study amino acids. Study intervention patients received significantly more protein on postoperative day 0; day 1; and day 2 compared with standard care patients ([Figure E2](#) in Online Data Supplement 2). No serious adverse events were reported.

Primary Outcomes: Measures of Renal Function

There was no significant difference with regard to the primary measure of renal function, duration of renal dysfunction, when standard care was compared with the amino

acid supplement group (0.65 vs 1.02 renal dysfunction days per 10 hospital days, 95% CI, -0.46 to 5.01 days, $P = .60$, [Table 2](#)). Covariate adjusted analysis also did not find any significant differences between groups (relative risk, 0.86; 95% CI, 0.19-3.79, $P = .84$, [Table 2](#) and [Table E1](#)).

Univariate analysis demonstrated a significant reduction in the duration of cardiac surgery-associated AKI attributable to the study amino acid supplement (0.45 vs 0.08 days of AKI per 10 hospital days, 95% CI, -0.43 to -0.04 days, $P = .037$, [Table 2](#)). Covariate-adjusted analysis confirmed the presence of this significant treatment effect (RR, 0.02; 95% CI, 0.005-0.11, $P < .0001$, [Table 2](#) and [Table E2](#)).

Estimated from serum creatinine-based equations,²⁰ repeated measures analysis demonstrated eGFR was significantly greater than baseline over the first 7 study days for patients receiving supplementary amino acids compared with standard care (+10.8% difference; 95% CI, 1.0%-20.8%, $P = .033$, [Figure 2](#)). Estimated from serum cystatin C-based equations,²¹ repeated measures analysis did not reach statistical significance (+5.0% difference; 95% CI, -5.2% to 15.1% , $P = .35$, [Figure E3](#) in Online Data Supplement 2). Cystatin C assay

TABLE 1. Baseline demographics and characteristics

Patient characteristics	Standard care, 36 patients	Amino acid supplement, 33 patients
Age, y, mean (SD)	70.8 (9.0)	72.3 (9.5)
Sex, female, n (%) [*]	5 (13.9%)	14 (42.4%)
Weight, kg, mean (SD)	86.2 (16.2)	88.8 (17.2)
Measures of kidney function		
Creatinine, $\mu\text{mol/L}$, mean (SD)	105.2 (31.1)	114.1 (39.0)
Renal dysfunction at baseline, creatinine $>168 \mu\text{mol/L}$, n (%)	1 (2.8)	4 (12.1)
Estimated GFR creatinine, mL/min/1.73 m^2 , mean (SD) ^{†,‡}	64.4 (18.6)	55.7 (20.2)
Estimated GFR cystatin C, mL/min/1.73 m^2 , mean (SD) ^{†,§}	55.6 (18.3)	45.7 (18.1)
History of CKD (stage 1 or greater), n (%) ^{†,}	16 (44.4)	22 (66.7)
Known risk factors for renal dysfunction, n (%)		
Nephrotoxic agent or pigment, over previous 24 h	0 (0)	0 (0)
Oliguria, over previous 24 h	0 (0)	1 (3.0)
Massive transfusion, over previous 24 h	0 (0)	0 (0)
Obstructive uropathy, over previous 24 h	0 (0)	0 (0)
Comorbidities, n (%)		
Hypertension, n (%)	33 (91.7)	29 (87.9)
Diabetes requiring insulin treatment, n (%)	5 (13.9)	7 (21.2)
Recent myocardial infarction, n (%)	12 (33.3)	7 (21.2)
Chronic lung disease, n (%)	2 (5.6)	5 (15.1)
Peripheral vascular disease, n (%) [†]	10 (27.8)	3 (9.1)
Any previous cardiac surgery, n (%)	7 (19.4)	4 (12.1)
Congestive heart failure, n (%) [¶]	22 (61.1)	24 (72.7)
NYHA class I, n (%) [†]	10 (45.5)	5 (20.1)
NYHA class II, n (%)	9 (40.9)	10 (41.7)
NYHA class III, n (%)	3 (13.6)	9 (17.5)
NYHA class IV, n (%)	0 (0)	0 (0)
Most recent LVEF, if recorded before surgery	56.9 (9.6) n = 32	56.1 (9.5) n = 28
Preoperative medications, n (%)		
Vasoactive drugs	1 (2.8)	0 (0)
NSAID (including aspirin $>160 \text{ mg/day}$)	1 (2.8)	3 (9.1)
ACE inhibitor	10 (27.8)	5 (15.1)
Proximal or distal loop diuretic	6 (16.7)	8 (24.2)
COX-2 inhibitor	0 (0)	0 (0)
Urgency of cardiac surgery, n (%)		
Elective	21 (58.3)	24 (72.7)
Urgent	15 (41.7)	9 (27.3)
Emergency	0 (0)	0 (0)
Salvage	0 (0)	0 (0)
Type of surgery, n (%) [†]		
CABG only	23 (63.9)	14 (42.4)
Valve only	9 (25)	15 (45.5)
Valve + CABG	4 (11.1)	2 (6.0)
Other procedure	0 (0)	2 (6.0)
Type of valve surgery, n (%)		
Mitral valve replacement	3 (8.6)	3 (9.1)
Mitral valve repair	1 (2.9)	2 (6.1)
Aortic valve replacement	9 (25.7)	13 (39.4)
Aortic valve repair	1 (2.9)	0 (0)
Pulmonary valve replacement	0 (0)	0 (0)
Pulmonary valve repair	0 (0)	0 (0)

(Continued)

TABLE 1. Continued

Patient characteristics	Standard care, 36 patients	Amino acid supplement, 33 patients
Tricuspid valve replacement	0 (0)	1 (3.0)
Tricuspid valve repair	0 (0)	1 (3.0)

SD, Standard deviation; GFR, glomerular filtration rate; CKD, chronic kidney disease; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; NSAID, nonsteroidal anti-inflammatory drug; ACE inhibitor, angiotensin-converting-enzyme inhibitor; COX-2 inhibitor, cyclooxygenase-2 inhibitor; CABG, coronary artery bypass graft. *Potential confounder due to imbalance ($P < .05$). †Potential confounder due to imbalance ($P < .15$). ‡GFR estimated from creatinine using the equations developed by Levey and colleagues.²⁰ §GFR estimated from cystatin C using the equations developed by Stevens and colleagues.²¹ ||Defined using Kidney Health Australia criteria: GFR < 60 mL/min/1.73 m² that is present for ≥ 3 months with or without evidence of kidney damage or evidence of kidney damage with or without decreased GFR as evidenced by the presence of albuminuria, hematuria after exclusion of urological causes, or structural or pathologic abnormalities on imaging or biopsy. ¶Defined using the NYHA classification based on severity of patient symptoms. Four classes range from class I: no limitation of physical activity to class IV: discomfort at rest and if any physical activity is undertaken, discomfort increases.

samples were obtained half as often as samples for serum creatinine.

Although total mean daily fluid intake did not differ between groups (2.3 ± 0.5 L/day vs 2.4 ± 0.4 L/day, $P = .21$) over the course of the ICU/HDU stay, mean daily urine output was significantly greater in the group of patients who received the amino acid supplement (1.4 ± 0.5 vs 1.7 ± 0.9 L/day, $P = .046$).

Repeated measures analysis revealed significantly greater blood urea levels in patients receiving the amino acid infusion (8.35 ± 8.33 mmol/L vs 11.39 ± 8.98 mmol/L, $P = .028$, Figure E4 in Online Data Supplement 2); however, there were no significant differences between groups in the use of RRT or any other measures of kidney function (Table 2).

Secondary Outcomes: Measures of Morbidity

There were no significant differences between groups with regard to survival, postoperative stroke, reoperation, ICU/HDU stay, hospital stay, or any other intraoperative or postoperative outcomes (Table 3).

DISCUSSION

In this pilot trial, we recruited patients with known presurgical eGFR less than 90 mL/min/1.73 m² who were scheduled to receive on-pump cardiac surgery to determine whether a simple and inexpensive amino acid infusion could protect their renal function. Our study process measures demonstrate that the provision of the amino acid infusion is feasible, and compared with the standard care group, achieves a significant increase in protein intake during the first 3 postoperative days. Although we found no significant effect on our primary measure of renal function, duration of renal dysfunction, commencing an infusion of standard L-amino acids immediately after the induction of anesthesia led to significant improvements in other key measures of renal function: duration of AKI was reduced, eGFR was improved, and urine output was increased. These improvements in key pre-stated secondary outcomes should be viewed as exploratory; however, they are potentially important and warrant confirmation by the conduct of multicenter clinical trials adequately powered

to detect improvements in patient-centered outcomes. See Video 1 for a brief talk about the overall relevance of these findings.

Measures of Renal Function

In the current study, a continuous infusion of amino acids commenced immediately after the induction of anesthesia and continued until discharge from ICU/HDU to the ward resulted in a sustained 10.8% (95% CI, 1.0%-20.8%) greater improvement in eGFR from baseline compared with patients receiving standard care (Figure 2). Young healthy adults can increase eGFR by 35% in response to a protein meal containing a dose of amino acids similar to the dose provided in this current pilot project,⁹ whereas healthy elderly subjects may increase eGFR by 15.7% in response to an infusion of amino acids.⁸

It is accepted that on-pump cardiac surgery exposes patients to numerous moderators and mediators that result in increased renal vascular resistance and reduced renal blood flow,^{3,4} thus predisposing patients to an increased risk of AKI.²⁶ Consuming a protein meal has been shown to decrease renal vascular resistance and increase renal blood flow in healthy adults.²⁷ Although we did not measure renal vascular resistance or renal blood flow in this pilot RCT, it remains a plausible mechanism of action to explain the documented treatment effects.

The primary measure of renal function used in this study was based on a creatinine threshold (>168 μ mol/L) accepted to define clinically significant renal dysfunction in critically ill patients in the ICU.^{17,18} Use of a threshold criteria allowed the assessment of treatment effectiveness in patients with preexisting and new-onset renal dysfunction. In 2013, the Kidney Disease: Improving Global Outcomes criteria defined AKI as “an abrupt decrease in kidney function” and required the documentation of a new-onset change in renal function from an explicitly identified baseline time period.¹⁹ Failure to find a significant effect on duration of renal dysfunction while documenting a significant reduction in duration of AKI suggests the modest improvement in eGFR documented in this pilot study may not be sufficient to return preexisting renal dysfunction to within normal

TABLE 2. Measures of renal function

	Standard care, 35 patients	Amino acid supplement, 33 patients	Effect magnitude (95% CI)	P value
Duration of renal dysfunction, creatinine >168 $\mu\text{mol/L}$, per 10 hospital days (95% CI)	0.65 days (0.27-1.53)	1.02 days (0.44-2.41)	0.37 days (−0.46 to 5.01)	.60
Covariate adjusted duration of renal dysfunction* creatinine >168 $\mu\text{mol/L}$, relative risk vs standard care (95% CI)			0.85 (0.19-3.79)	.84
Duration of AKI,† creatinine increase >26.5 $\mu\text{mol/L}$ within 48 h or > 1.5 $\times$ baseline within 7 days of surgery, per 10 hospital days (95% CI)	0.45 days (0.19-1.04)	0.08 days (0.03-0.17)	−0.37 days (−0.43 to −0.04)	.037
Covariate adjusted duration of AKI‡ creatinine increase >26.5 $\mu\text{mol/L}$ within 48 h or >1.5 $\times$ baseline within 7 days of surgery, relative risk vs standard care (95% CI)			0.02 (0.005-0.11)	<.0001
Severity of AKI, days (95% CI), per 10 hospital days (95% CI)				
Duration of stage 1 AKI, creatinine increase >26.5 $\mu\text{mol/L}$ within 48 h or >1.5 and <2 $\times$ within 7 days of surgery	0.37 days (0.17-0.83)	0.08 days (0.03-0.17)	−0.29 days (−0.36 to −0.00)	.0497
Duration of stage 2 AKI, creatinine ≥ 2 and <3 $\times$ within 7 days	0.08 days (0.05-0.14)	0 days (0 to 0)	NE	NE
Duration of stage 3 AKI, creatinine $\geq 3\times$ or $\geq 353.6 \mu\text{mol/L}$ within 7 days	0.04 days (0.02-0.07)	0 days (0-0)	NE	NE
Duration of RRT, mean per patient (95% CI), ICU/HDU days	0.14 days (0.03-0.60)	0.84 days (0.20-3.5)	0.70 days (−0.9 to 14.6)	.22
Patients with renal dysfunction, creatinine >168 $\mu\text{mol/L}$, %, (n/N)	17.1% (6/35)	18.2% (6/33)	1.0% (−22.1 to 24.9)	1.00
Patients with AKI, creatinine >1.5 $\times$ baseline, %, (n/N)	20.0% (7/35)	9.0% (3/33)	−10.9% (−33.3 to 13.4)	.30
Severity of AKI, %, (n/N)				
Patients with stage 1 AKI	20.0% (7/35)	9.0% (3/33)	−10.9% (−33.3 to 13.4)	.30
Patients with stage 2 AKI	2.9% (1/35)	0% (0/33)	−2.9% (−26.6 to 21.2)	1.00
Patients with stage 3 AKI	2.9% (1/35)	0% (0/33)	−2.9% (−26.6 to 21.2)	1.00
Patients receiving RRT, %, (n/N)	2.9% (1/35)	12.1% (4/33)	9.3% (−3.2 to 21.7)	.19
Requiring RRT at study day 90, % (n/N)	3.0% (1/33)	0% (0/31)	−3.0% (−27.4 to 21.8)	1.00
Total fluid volume, per patient per ICU/HDU day, mL, mean (SD)	2304 (516)	2447 (407)	142 (−84 to 369)	.21
Urine output, per patient per ICU/HDU day, mL, mean (SD)	1383 (478)	1733 (858)	349 (7-691)	.046
Net fluid balance, per patient per ICU/HDU day, mL, mean (SD)	921 (643)	686 (790)	−234 (−587 to 118)	.19
Oliguria, <100 mL for 6 consecutive h, mean per patient (95% CI), ICU/HDU days	0.11 days (0.04-0.27)	0.36 days (0.15-0.86)	0.24 days (−0.49 to 1.93)	.19
Diuretic use, any loop diuretic, mean per patient (95% CI), ICU/HDU days	2.30 days (1.44-3.62)	1.97 days (1.24-3.12)	−0.31 days (−1.50 to 2.66)	.75

CI, Confidence interval; AKI, acute kidney injury; NE, not estimable; RRT, renal-replacement therapy; ICU/HDU, intensive care unit/high-dependency unit; SD, standard deviation. *Covariate-adjusted model controlled for confounding due to baseline creatinine, peripheral vascular disease, and the stratification variable, baseline eGFR <30 mL/min/1.73 m². †Defined using the Kidney Disease Improving Global Outcomes criteria. Baseline creatinine was established using a presurgical blood sample. ‡Covariate-adjusted model controlled for confounding due to baseline renal dysfunction, chronic kidney disease, and the stratification variable, baseline eGFR <30 mL/min/1.73 m².

$P = .033$ between groups from baseline covariate adjusted repeated measures analysis

FIGURE 2. Estimated glomerular filtration rate by study day for patients randomly allocated to receive a continuous infusion of amino acids or standard care: percent change from presurgery baseline. Glomerular filtration rate estimated using the Chronic Kidney Disease Epidemiology Collaboration serum creatinine equations developed by Levey and colleagues.²⁰ $P = .033$ for between-group difference from baseline covariate-adjusted repeated measures analysis. Error bars indicate 95% confidence intervals around differences between groups at each time point. Sx, Surgery.

parameters but may be sufficient to confer protection against new-onset kidney injury.

Major observational studies consistently demonstrate that duration of AKI is associated with meaningful patient-centered outcomes. In a cohort of 4987 patients undergoing cardiac surgery, increasing duration of AKI was shown to be significantly associated with decreasing duration of survival over 5-year follow-up: as the observed duration of AKI increased from 2 days to more than 7 days, the death rate doubled during each year of follow-up.²⁸ In addition, a 1111-patient study demonstrated that more rapid recovery of renal function after the onset of cardiac surgery-associated AKI was significantly associated with improved 3-year survival,²⁹ whereas a 3245-patient study demonstrated that if cardiac surgery-associated AKI persisted until time of hospital discharge, patients were 15 times more likely to develop chronic kidney disease stage 4 to 5 within 2 years of their surgery.³⁰

In the US health care system, the direct hospital costs associated with caring for a cardiac surgery patient who develops AKI are estimated to be \$38,358 greater than the costs associated with caring for a similar cardiac surgery patient who does not develop AKI.² Furthermore, progression to chronic kidney disease requiring long-term RRT or renal transplantation may increase annual medical costs beyond established willingness-to-pay thresholds.^{31,32}

Any reduction in the incidence or duration of AKI may translate to meaningful patient benefits and reduce the consumption of scarce resources.

Strengths and Limitations

This paper presents the results of a small, single-center pilot RCT. As such, estimates of treatment effects may be overoptimistic and/or unique to the population studied. However, the results demonstrate the study intervention is feasible and has promising effects on multiple measures of renal function. Furthermore, there is no objective evidence to suggest the study population is unique. However, as with all pilot projects, our findings remain exploratory and hypothesis generating. Future research is needed to confirm our results and to determine whether our findings generalize to patient groups not explicitly enrolled in this small pilot RCT.

Two patients were not recruited into the study after randomization because they had procedures rescheduled to off-pump cardiac surgery. The onset of AKI is known to be significantly lower after off-pump cardiac surgery compared with on-pump cardiac surgery.²⁶ Thus, the exclusion of these 2 patients is unlikely to bias the results in favor of the study intervention. Furthermore, the study intervention was not commenced in either of these patients because the ethics committee approved protocol

TABLE 3. Secondary outcomes

	Standard care, 36 patients	Amino acid supplement, 33 patients	Difference (95% CI)	P value
Intraoperative outcomes				
Pump time, min, mean (SD)	286 (147)	248 (121)	−38 (−101 to 25)	.24
Crossclamp time, min, mean (SD)	136 (71)	112 (52)	−24 (−53 to 5)	.11
Total time of surgery, min, mean (SD)	373 (143)	313 (95)	−60 (−119 to 1)	.05
Number of vessels bypassed, if CABG, mean (SD)	3.4 (1.2) n = 27	2.8 (0.9) n = 16	−0.6 (−1.2 to 0.1)	.07
Vasoactive drug use, % (n/N)	100% (36/36)	100% (33/33)	0.0%	1.00
Total fluids delivered, mL, mean (SD)	3333 (1983)	2736 (1643)	−597 (−1467 to 273)	.18
Study amino acids delivered, mL, mean (SD)	0 (0)	223 (69)	223 (199-246)	N/A
Urine output, mL, mean (SD)	512 (327)	624 (588)	112 (−115 to 339)	.34
Postoperative outcomes				
ICU stay, days, mean (95% CI)	3.3 (2.6-4.0)	4.1 (3.3-5.0)	0.8 (−0.6 to 2.9)	.30
HDU stay, days, mean (95% CI)	1.8 (1.4-2.3)	1.6 (1.3-2.1)	−0.2 (−0.8 to 0.9)	.72
Hospital stay, days, mean (95% CI)	14.4 (12.5-16.6)	12.2 (10.6-14.0)	−2.2 (−5.2 to 1.8)	.25
Mechanical ventilation, days, mean (95% CI)	2.31 (1.83-2.92)	2.39 (1.89-3.02)	0.07 (−0.81 to 1.51)	.89
Vasoactive drug use, % (n/N)	100% (35/35)	96.9% (32/33)	−3.0% (−8.8 to 3.0)	.48
Duration of vasoactive drug use, days, mean (95% CI)	3.1 (2.7-3.6)	3.1 (2.7-3.5)	0.0 (−0.8 to 0.9)	.74
Low cardiac output syndrome,* % (n/N)	5.7% (2/35)	0 (0/33)	−5.7% (−29.2 to 18.5)	.49
Reoperation, % (n/N)	17.1% (6/35)	9.1% (3/33)	−8.0% (−30.5 to 16.3)	.47
Antimicrobial changed,† % (n/N)	94.3% (33/35)	100% (33/33)	5.7% (−18.5 to 29.2)	.49
Atrial fibrillation, % (n/N)	31.4% (11/35)	33.3% (11/33)	1.9% (−22.1 to 24.9)	1.00
Ventricular fibrillation or ventricular tachycardia, % (n/N)	2.9% (1/35)	6.1% (2/33)	3.2% (−20.6 to 27.1)	.61
CPR for cardiac/respiratory arrest, % (n/N)	0% (0/35)	0% (0/33)	0%	1.00
Stroke, % (n/N)	2.9% (1/35)	3.0% (1/33)	0.1 (−4.1 to 7.9)	1.00
Patient-centered outcomes				
Alive at ICU discharge, % (n/N)	97.2% (35/36)	93.9% (31/33)	−3.2% (−26.3 to 20.5)	.60
Alive at hospital discharge, % (n/N)	97.2% (35/36)	93.9% (31/33)	−3.2% (−26.3 to 20.5)	.60
Alive at Day 90, % (n/N)	97.2% (35/36)	93.9% (31/33)	−3.2% (−26.3 to 20.5)	.60
RAND-36 General Health, reported by survivors at day 90, mean (SD)	67.1 (27.6) 35 survivors	54.8 (26.2) 31 survivors	−12.3 (−0.97 to 25.5)	.07
RAND-36 Physical Function, reported by survivors at day 90, mean (SD)	71.9 (30.5) 35 survivors	63.9 (26.5) 31 survivors	−8.0 (−22.0 to 6.0)	.26
ECOG performance status, reported by survivors at day 90, mean (SD)	0.80 (0.96) 35 survivors	0.83 (0.69) 31 survivors	0.04 (−0.37 to 0.45)	.85

CI, Confidence interval; SD, standard deviation; CABG, coronary artery bypass graft; N/A, not available; ICU, intensive care unit; HDU, high-dependency unit; CPR, cardiopulmonary resuscitation; RAND-36, Public domain version of the Short Form 36; ECOG, Eastern Collaborative Oncology Group. *Defined as cardiac index less than 2 L/min/m² with objective signs of an imbalance between oxygen delivery and oxygen consumption (pH < 7.3). †Antimicrobial changed during ICU/HDU stay, indicating concern regarding potential infection.

stipulated on-pump surgery as an explicit eligibility criterion.

Another potential limitation of this study is that the intervention was not blinded. However, measures of renal function were based on objective assays conducted by a central lab that was unaware of treatment allocation. In addition, treatments such as use of diuretics and provision of RRT did not differ between study groups. There is no objective evidence of bias arising due to lack of intervention blinding.

Although the standard assay for serum creatinine, and estimation of GFR using creatinine-based equations, may be biased by large positive shifts in fluid balance, creatinine unadjusted for fluid balance remains the clinical

standard for the diagnosis of cardiac surgery-associated AKI.^{3,26} Failure to adjust for large positive fluid balances inherent with cardiac surgery may result in the underdiagnosis of AKI and over-estimation of eGFR.³³ Since fluid intake and net fluid balance did not differ between randomized groups (Table 2), it is unlikely that failure to adjust for accumulated fluid balance resulted in false positive results.

Caveat for Future Research

It is important to recognize that metabolism of the study amino acid supplement led to a statistically significant increase in blood urea levels (ureagenesis). Future investigators need to be cautioned to monitor blood urea

VIDEO 1. Prof Rinaldo Bellomo talks about the project. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)33243-4/fulltext](https://www.jtcvs.org/article/S0022-5223(18)33243-4/fulltext).

levels closely. If clinicians become concerned, we strongly recommend the study intervention should be stopped to give urea a chance to clear before RRT is considered.

CONCLUSIONS

As defined by the 2016 extension to the CONSORT statement, the purpose of a pilot trial is “to support the development of a future definitive RCT.”¹⁴ This small pilot trial demonstrates that the provision of the study intervention, an amino acid infusion commenced after the induction of anesthesia, is feasible and achieves a significant increase in protein intake during the first 3 postoperative days. Although the study intervention did not alter duration of renal dysfunction, it did result in a significant reduction in the duration of AKI and also resulted in improvements in other key measures of renal function. Because the clinical relevance of these improvements in renal function remains unclear, these findings warrant confirmation by the conduct of multi-center clinical trials adequately powered to detect improvements in patient-centered outcomes.

Conflict of Interest Statement

Dr Doig reports receiving academic research grants from Fresenius Kabi Deutschland GmbH and Baxter Healthcare Pty Ltd and speakers honoraria from Fresenius Kabi Deutschland GmbH, Baxter Healthcare Australia, Pty Ltd, Nestle Healthcare, Vevy, Switzerland, and Nutricia Pharmaceutical (Wuxi) Co, Ltd, China. Dr Allingstrup reports receiving academic research grants from Fresenius Kabi Deutschland GmbH, Medinor A/S Denmark, and COSMED Irl, Rome, Italy, and speakers honoraria from Fresenius Kabi A/S Denmark, Baxter Healthcare A/S Denmark, and Nutricia A/S Denmark. Dr Pollock reports receiving consulting fees from Baxter Healthcare Pty, Ltd, on an unrelated research project. All other authors have nothing to disclose with regard to commercial support.

Heart Research Australia, The University of Sydney's Cardiothoracic Research Scheme, and/or Baxter Healthcare Pty, Ltd, played no role in the design or conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript. Although the participating site was compensated for the costs of conducting the trial, site investigators did not receive financial compensation for their contributions.

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Key Words: randomized controlled trial, acute kidney injury, cardiac surgery, amino acids, pilot