



Efficacy and Safety of a Balanced Salt Solution Versus a 0.9% Saline Infusion for the Prevention of Contrast-Induced Acute Kidney Injury After Contrast-Enhanced Computed Tomography

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Rationale & Objective: We aimed to elucidate whether a balanced salt solution decreases the occurrence of contrast-induced acute kidney injury (CI-AKI) after contrast-enhanced computed tomography (CE-CT) as compared to 0.9% saline solution.

Study Design: A randomized clinical trial.

Setting & Participants: The study was performed in 14 tertiary hospitals in South Korea. Patients with estimated glomerular filtration rates (eGFRs) < 45 or < 60 mL/min/1.73 m² and additional risk factors (age ≥ 60 years or diabetes) who were undergoing scheduled CE-CT were included from December 2016 to December 2018.

Intervention: An open-label intervention was performed. The study group received a balanced salt solution and the control group received 0.9% saline solution as prophylactic fluids for CE-CT.

Outcomes: The primary outcome was CI-AKI, defined by creatinine level elevation ≥ 0.5 mg/dL or 25% from baseline within 48 to 72 hours after CE-CT. Secondary outcomes included AKI defined based on the KDIGO (Kidney Disease: Improving Global Outcomes) guideline, eGFR

changes, death, or requiring dialysis within 6 months after CE-CT.

Results: 493 patients received the study fluids. The control and study groups included 251 and 242 patients, respectively. The occurrence of CI-AKI in the study (10 [4.2%]) and control (17 [6.8%]) groups was not significantly different ($P = 0.27$). No significant difference was present for the secondary outcomes; AKI by the KDIGO definition (study: 19 [7.9%], control: 27 [10.8%]; $P = 0.33$), death/dialysis (study: 11 [4.7%], control: 9 [3.7%]; $P = 0.74$), and eGFR changes (study: 0.1 ± 0.2 mg/dL, control: 0.3 ± 2.8 mg/dL; $P = 0.69$).

Limitations: This study failed to meet target enrollment.

Conclusions: The risk for CI-AKI was similar after administration of a balanced salt solution and after use of 0.9% saline solution during CE-CT in higher-risk patients.

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Trial Registration: Registered at [ClinicalTrials.gov](https://clinicaltrials.gov) with study number NCT02799368.

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Contrast-induced acute kidney injury (CI-AKI) is one of the most common iatrogenic kidney injuries.¹ Moreover, CI-AKI has been associated with increased risk for mortality, longer hospital stays, and end-stage kidney disease in patients, particularly those with chronic kidney disease.¹⁻⁴ Therefore, early diagnosis or prevention of CI-AKI remains an important medical issue.

The prophylactic measures for CI-AKI have long been debated. Intravenous administration of 0.9% saline solution has been reported as an essential part of CI-AKI prevention.^{5,6} However, effort has been made to find an alternative because 0.9% saline solution contains supra-physiologic levels of chloride and has a relatively acidic pH, which may lead to kidney vasoconstriction.⁷ No current evidence supports the use of different fluids to prevent CI-AKI, although there have been reports showing that a balanced salt solution,⁸⁻¹² which contains

a physiologic amount of chloride and has neutral pH, was beneficial in other clinical settings. However, a recent trial also demonstrated that implementing 0.9% saline solution in CI-AKI prevention did not provide any benefits to patients when compared with those who received no preventive prophylactics before contrast-enhanced computed tomography (CE-CT).¹³ Therefore, the necessity for a better prophylactic measure for CI-AKI is evident, particularly for high-risk patient groups in which prevention may still have clinical benefits.

In this multicenter randomized controlled trial, we aimed to compare the effectiveness of a balanced salt solution and 0.9% saline solution in preventing CI-AKI. We hypothesized that the balanced salt solution may be a similar or better prophylactic method for CI-AKI after CE-CT than 0.9% saline solution.

METHODS

Ethical Considerations

All patients were aware of the nature of the study at the time of enrollment and provided written informed consent. The study was performed in accordance with the Declarations of Helsinki. The Ministry of Food and Drug Safety of the Republic of Korea and the institutional review boards of the study hospitals approved this study (Seoul National University Hospital: H-1605-156-766, Kyungpook National University Hospital: KNUH 2016-09-007, National Medical Center: H-1608-069-004, National Health Insurance Service Ilsan Hospital: NHIMC 2016-10-010-002, Seoul National University Bundang Hospital: B-1609/363-401, Bundang Cha Hospital: 2016-09-011-002, Seoul St. Mary's Hospital: KC16MIMT0741, Seoul National University Boramae Hospital: 16-2016-126, Severance Hospital: 4-2016-0691, Ewha Womans University Mokdong Hospital: 2016-10-014, Incheon St. Mary's Hospital: IS16MIMT0033, Gachon University Gil Medical Center: GAIRB2016-322, Samsung Medical Center: 2018-01-024, and Ajou University Hospital: AJIRB-MED-CT3-18-008).

Study Design and Study Population

This was a randomized, open-label, active-control, 2-parallel-group, multicenter, phase 3 study. Details of the study design and protocol have been published previously.¹⁴ In brief, the study included participants from 14 tertiary hospitals in the Republic of Korea. We recruited patients who were scheduled for CE-CT in outpatient settings but had risk factors for CI-AKI. Inclusion criteria were: (1) adult patients (aged ≥ 18 years); (2) baseline estimated glomerular filtration rate (eGFR), measured within 3 months, < 45 mL/min/1.73 m² or both having a baseline eGFR < 60 mL/min/1.73 m² and either one of the following risk factors: diabetes mellitus or age 60 years or older¹⁵; and (3) ability to provide informed consent and adequate information for the end point assessment. We excluded those who had end-stage kidney disease, significant heart failure, and other conditions that made receiving contrast materials or the study fluids inappropriate.

Exclusion criteria were: (1) baseline eGFR < 15 mL/min/1.73 m² or receiving dialysis; (2) heart failure with left ventricular ejection fraction $< 45\%$ or severe symptoms (New York Heart Association functional classification III or IV); (3) co-existing acute pulmonary edema or decompensated heart failure requiring the following medications: dobutamine, dopamine, milrinone, amrinone, or nesiritide; (4) serum potassium level > 5.5 mEq/L or serum sodium level > 145 mEq/L at the screening period or within 3 months before the CT; (5) history of intravenous or intra-arterial contrast agent administration within 1 week; (6) previous history of hypersensitivity reaction to the iodinated contrast agent; (7) history of multiple myeloma; (8) women who are currently

pregnant/breastfeeding or planning to become pregnant; (9) patients with an expected survival duration less than 6 months; and (10) enrollment in another clinical trial.

Intervention and Randomization

The main intervention was intravenous administration of specific fluids for CI-AKI prevention. The study group received a balanced salt solution (Plasma solution A; CJ Healthcare) with 98 mEq/L of chloride at pH 7.4, and the control group received 0.9% saline solution with 154 mEq/L of chloride at pH 6.0. Both fluids were manufactured by the same company. Both fluids were infused at a rate of 3 mL/kg per hour for 1 hour before and 1.5 mL/kg per hour for 4 hours after the CE-CT. Although the volume or infusion protocol of contrast materials used for the CE-CT was not controlled, all study hospitals used iso- or low-osmolar iodinated contrast materials. N-Acetylcysteine was not used as a supplemental medication due to limited benefits for CI-AKI prevention. Restrictions were not applied for other coadministered medications.

Study randomization was performed in a 1:1 manner with simple randomization. The randomization list was generated using a professional on-line randomization service (Sealed Envelope, London, UK).

Sample Size and Patient Enrollment

CI-AKI incidence was predicted to be 11.5% in the control group according to the previous prospective study.⁷ Because there was no study regarding the incidence of CI-AKI with prevention by using a balanced solution at the time of study planning, the expected CI-AKI incidence of the study group was adapted from a previous study in another clinical setting and was predicted to be 8.4%.¹¹ The sample size goal was 1,328 study participants, 664 in each group, which was calculated from a noninferiority limit of 1.5% with power of at least 80% and 1-side type 1 error rate of 2.5%. Allowing a 20% withdrawal rate in each group, a total of 1,660 participants were needed. Patient enrollment was scheduled for 2 years from the first patient registration.

Study Outcomes

The primary end point was the occurrence of CI-AKI, which was defined as serum creatinine level elevation ≥ 0.5 mg/dL or $\geq 25\%$ from baseline at the follow-up visit 48 to 72 hours after CE-CT. Secondary end points included: (1) eGFR reduction at the follow-up visit; (2) AKI according to the KDIGO (Kidney Disease: Improving Global Outcomes) criteria, which was serum creatinine level elevation ≥ 0.3 mg/dL or 50% from baseline at the follow-up visit⁵; and (3) death or requiring dialysis within 6 months of the CE-CT. Safety assessment was done primarily by collecting data for adverse events or determined by clinical assessments, including abnormalities in laboratory test results or vital signs.

Statistical Analyses

Among randomly assigned patients, all who received the allocated intervention were included in the full analysis set. The per-protocol set consisted of patients who ended the trial period without a violation of the study protocol. Results from the full analysis set are presented, and results from the per-protocol set are not described unless significantly different.

We presented categorical variables as number with percent and continuous variables as mean \pm standard deviation. Categorical variables were analyzed using χ^2 test. Continuous variables were analyzed using t test. The noninferiority of the study group for the primary outcome was investigated with the noninferiority test with a 1-sided P value. Additional adjustments for baseline characteristics were performed for a multivariable logistic regression model, and the model was adjusted for age, sex, histories of hypertension and diabetes, baseline eGFR, and urine protein-creatinine ratio. We performed complete-case analysis, and patients with missing values were not included in the analysis, accordingly. Multivariable adjustment for continuous variables was performed using analysis of covariance adjusted for the same covariates described. All analyses were performed using R software

(version 3.6.2; the R Foundation). Except for the non-inferiority test, 2-sided $P < 0.05$ was considered statistically significant.

RESULTS

Patient Enrollment

The first patient enrolled on December 14, 2016. At the end of the enrollment period, 619 patients were randomly assigned and 493 patients received the study fluids (Fig 1). Enrollment did not increase despite significant efforts to facilitate patient recruitment and expansion of the inclusion criteria, and the study was closed without further patient registration. The study results were decided to be reported because the data were considered to have certain clinical value and may be referred to by future studies.

Baseline Characteristics

Among patients who received fluids, 251 patients in the control group received 0.9% saline solution and 242 patients in the study group received a balanced salt solution. Baseline characteristics, demographics, baseline coadministration of other medications, and laboratory result profiles were well balanced between the 2 groups (Table 1),

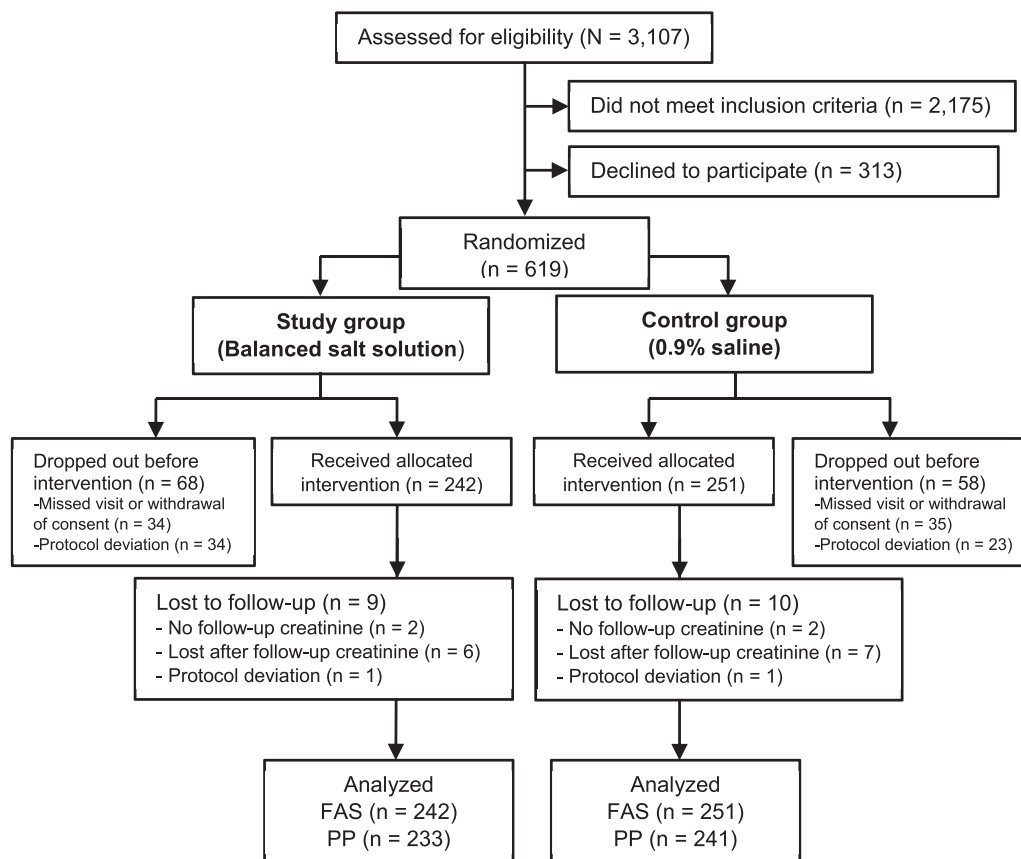


Figure 1. The Consolidated Standards of Reporting Trials (CONSORT) study flow diagram. Abbreviations: FAS, full analysis set; PP, per protocol.

Table 1. Baseline Characteristics of the Study Population

	0.9% Saline Solution (N = 251)	Balanced Salt Solution (N = 242)
Demographic Findings		
Age, y	70.6 ± 10.2	71.3 ± 10.4
Male sex	178 (70.9%)	167 (69.0%)
Height, cm	162.2 ± 7.9	162.3 ± 8.1
Weight, kg	63.7 ± 11.0	63.9 ± 10.2
Comorbid Conditions and Medication History		
Hypertension	200 (79.7%)	171 (70.7%)
Diabetes mellitus	135 (53.8%)	106 (43.8%)
RAAS inhibitor	107 (42.6%)	93 (38.4%)
β-Blocker	51 (20.9%)	46 (19.3%)
Calcium channel blocker	99 (40.6%)	90 (37.8%)
Metformin	37 (15.0%)	29 (12.2%)
Insulin	25 (10.1%)	18 (7.6%)
Other diabetes medications	84 (34.1%)	60 (25.3%)
Statin	97 (39.6%)	98 (41.2%)
Diuretics	54 (22.0%)	46 (19.3%)
NSAID	30 (12.2%)	25 (10.5%)
CE-CT contrast amount, mL	119.0 ± 29.0	116.6 ± 27.8
Baseline Laboratory Values		
Systolic BP, mm Hg	130.8 ± 16.6	130.7 ± 16.3
Diastolic BP, mm Hg	73.7 ± 10.9	74.4 ± 12.2
Hemoglobin, g/dL	11.8 ± 2.0	11.8 ± 2.0
Sodium, mEq/L	139.7 ± 3.0	139.5 ± 3.0
Potassium, mEq/L	4.6 ± 0.5	4.6 ± 0.6
Chloride, mEq/L	105.2 ± 3.7	105.4 ± 4.5
Total CO ₂ , mEq/L	23.8 ± 3.5	23.8 ± 3.6
SUN, mg/dL	26.0 ± 11.7	26.0 ± 10.9
Creatinine, mg/dL	1.6 ± 0.6	1.6 ± 0.6
eGFR, mL/min/1.73 m ²	45.2 ± 13.1	46.1 ± 13.1
Protein, g/dL	7.0 ± 0.7	7.0 ± 0.7
Albumin, g/dL	4.0 ± 0.6	4.0 ± 0.5
Urinary PCR, mg/g	178.6 ± 837.6	231.0 ± 1159.2

Note: Values for categorical variables are given as number (percent); values for continuous variables are given as mean ± standard deviation. Conversion factors for units: creatinine in mg/dL to μmol/L, ×88.4; SUN in mg/dL to mmol/L, ×0.357.

Abbreviations: BP, blood pressure; CE-CT, contrast-enhanced computed tomography; CO₂, carbon dioxide; eGFR, estimated glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drug; PCR, protein-creatinine ratio; RAAS, renin-angiotensin-aldosterone system; SUN, serum urea nitrogen.

except that the control group had a higher proportion of patients with hypertension or diabetes mellitus.

Patient Outcomes

Four patients missed their follow-up creatinine measurements. CI-AKI occurred in 10 (4.2%) patients in the study group and 17 (6.8%) in the control group (Table 2). The balanced salt solution showed noninferior risks for CI-AKI when compared with the control group (*P* for noninferiority < 0.001). However, no statistical significance was identified with the incidence of CI-AKI (*P* = 0.27), AKI using the KDIGO definition (*P* = 0.33),

Table 2. Univariable Analysis Results for the Study Outcomes

	0.9% Saline Solution (N = 251) ^a	Balanced Salt Solution (N = 242) ^a	<i>P</i>
CI-AKI	17 (6.8%)	10 (4.2%)	0.27
Absolute change in eGFR, mg/dL	0.3 ± 2.8	0.1 ± 0.2	0.69
AKI by KDIGO definition	27 (10.8%)	19 (7.9%)	0.33
Death/dialysis within 6 mo	9 (3.7%)	11 (4.7%)	0.74

Note: Values for categorical variables are given as number (percent); values for continuous variables are given as mean ± standard deviation.

Abbreviations: AKI, acute kidney injury; CI-AKI, contrast-induced acute kidney injury; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

^aTwo patients in the study group and 2 patients in the control group missed the follow-up visits for creatinine measurement. Six patients in the study group and 7 patients in the control group did not receive assessment for death/dialysis within 6 months.

or death/ dialysis within 6 months from CE-CT (*P* = 0.74). Absolute changes in eGFRs at the follow-up visit were also similar (*P* = 0.69).

When we adjusted for age, sex, history of diabetes and hypertension, baseline eGFR, and urinary protein-creatinine ratio values (Table 3), the difference in outcomes between the 2 groups did not reach statistical significance; CI-AKI (adjusted odds ratio [OR], 78 [95% CI, 0.31-1.89]; *P* = 0.58), AKI by KDIGO definition (adjusted OR, 0.93 [95% CI, 0.45-1.87]; *P* = 0.83), death/dialysis (adjusted OR, 1.29 [95% CI, 0.49-3.50]; *P* = 0.61), and eGFR changes (*P* = 0.61).

Clinical characteristics including age (interaction *P* = 0.44), sex (interaction *P* = 0.19), history of diabetes (interaction *P* = 0.38) or hypertension (interaction *P* = 0.99), eGFR (interaction *P* = 0.17), or urinary protein-creatinine ratio (interaction *P* = 0.69) values did not show significant interaction with the association between preventive fluid use and risk for CI-AKI. Therefore, no subgroup analysis was performed.

Safety

Four adverse events occurred from the time of fluid administration and CE-CT until the initial follow-up visits, and no deaths occurred. There were 2 cases of gastrointestinal symptoms or pneumonia that were not considered to be related to the fluid administration or

Table 3. Multivariable Logistic Regression Analysis Results

	Adjusted OR (95% CI)	<i>P</i>
CI-AKI	0.78 (0.31-1.89)	0.58
AKI by KDIGO definition	0.93 (0.45-1.87)	0.83
Death/dialysis within 6 mo	1.29 (0.49-3.50)	0.61

Note: ORs were adjusted for baseline age, sex, history of diabetes, hypertension, baseline estimated glomerular filtration rate, and urinary protein-creatinine ratio. The reference group was the control group that received 0.9% saline solution, and the study group received a balanced salt solution.

Abbreviations: AKI, acute kidney injury; CI, confidence interval; CI-AKI, contrast-induced acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; OR, odds ratio.

CE-CT. There was 1 case of suspected pulmonary edema in the study group that resolved after a week of hospitalization. There was 1 patient requiring acute dialysis due to possible CI-AKI in the study group that resolved after a few dialysis sessions without proceeding to maintenance dialysis.

DISCUSSION

In this randomized clinical trial, risk for CI-AKI was similar after the use of a balanced salt solution and after use of 0.9% saline solution during CE-CT within the limited number of high-risk patients. However, the primary and secondary outcomes did not improve with the balanced salt solution, and a similar safety profile was observed. Although our trial registration did not meet the initially planned enrollment number, our study suggests that use of a balanced salt solution may be noninferior to the use of 0.9% saline solution regarding the risk for CI-AKI. However, no additional benefits of the administration of a balanced salt solution was proven for CI-AKI prevention after CE-CT.

CI-AKI remains an important clinical issue because use of iodine contrast is common in many interventions and diagnostic procedures, and it has been reported to be associated with an increased risk for adverse patient outcomes.^{1,2,6,16,17} CI-AKI after CE-CT has different characteristics than AKI after intra-arterial contrast material administration because most patients in the former are in a relatively stable medical condition and the amount of the contrast material is controlled, leading to a low incidence.¹ However, CI-AKI after CE-CT has been reported to be associated with worse patient prognosis.^{3,18} Contrarily, the recent multicenter AMACING clinical trial showed that use of 0.9% saline solution was similar to taking no preventive measures with respect to the incidence of CI-AKI after CE-CT.¹³ Therefore, the efficacy of 0.9% saline solution has been questioned, and additional investigation for a better prophylactic method is warranted, particularly in a patient group with higher risk for CI-AKI.

In this clinical trial, we tested the efficacy and safety of a balanced salt solution, which has shown better outcomes than normal saline solution in other clinical settings,¹¹ for CI-AKI prevention in patients undergoing CE-CT. Our patient group had multiple risk factors or severely decreased kidney function; thus, we aimed to assess the use of a balanced salt solution in a patient group with a prominent risk for CI-AKI. Although the study failed to meet the target number of participants, in the non-negligible number of the finally studied patients, the balanced salt solution group showed similar risk for CI-AKI and other secondary outcomes when compared with the 0.9% saline solution group. The study suggested that a balanced salt solution may be noninferior to 0.9% saline solution regarding the risk for CI-AKI, but whether the

specific benefits of the fluid for CI-AKI after CE-CT exist has not been answered here.

The balanced salt solution may provide benefits over 0.9% saline solution because it contains physiologic levels of chloride, decreasing the possibility of developing metabolic acidosis.^{8,9} Similar expectations were present regarding the use of sodium bicarbonate fluids, but recent trials have shown that the benefits of sodium bicarbonate are uncertain.^{7,19,20} Recent studies in critical care settings or with health volunteers have suggested the benefits of the balanced salt solution.^{8,9,11} A clinical trial was performed using perioperative fluids, but the trial did not demonstrate any benefits of using a balanced salt solution for patients who underwent surgery.¹² Our patients were more clinically stable than those in other settings, and we considered that in such a clinical environment, the pure effect of a prophylactic fluid administration could be revealed. However, use of a balanced salt solution did not show additional benefits for CI-AKI prevention in this trial with a considerable number of patients, and thus the advantage of a balanced solution over 0.9% saline solution is still in question.

Our study has several limitations. First, the study did not meet the calculated number of patients needed to be appropriately powered. The robust statistical confirmation of our trial cannot be guaranteed due to its low power; thus, our study results can only address the possibilities. With the reported incidence of CI-AKI in our study, 968 patients with follow-up completion would be necessary for an adequately powered noninferiority trial. However, our study results may be referred to when designing a further trial or be implemented in a meta-analysis searching for an appropriate measure in the field of CI-AKI prophylaxis.

Second, our study did not address potential benefits of prevention of CI-AKI during CE-CT over no prevention. After the recent report from the AMACING trial, the benefits of CI-AKI prophylactic measure during CE-CT itself has been questioned. Thus, a future clinical trial may consider including a control group without intervention and testing whether a prophylactic method, even the use of 0.9% saline solution, is practically necessary before performing CE-CT in clinically stable patients. In addition, because CI-AKI risk after CE-CT is relatively low, such a future trial could target a patient group with higher risks of CI-AKI or those who receive cardiovascular procedures using iodine contrasts.

Last, the study was performed in South Korea with little ethnic diversity; thus, our study cannot be generalized to patients of non-Asian ethnicity.

In conclusion, in this trial with limited study enrollment, use of a balanced salt solution during CE-CT may be noninferior to the use of 0.9% saline solution regarding the risk for CI-AKI. Whether there are clinical benefits of a balanced salt solution over 0.9% saline solution remains uncharacterized. Further studies demonstrating an efficacy-proven CI-AKI prevention method are warranted.

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