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NEPHROLOGY - ORIGINAL PAPER

Left ventricular end-diastolic pressure-guided hydration for the prevention of contrast-induced acute kidney injury in patients with stable ischemic heart disease: the LAKESIDE trial

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Abstract

Objectives Contrast-induced acute kidney injury (CI-AKI) is a serious complication in patients undergoing diagnostic cardiac angiography or percutaneous coronary intervention. We aimed to evaluate the preventive effects of left ventricular end-diastolic pressure (LVEDP)-guided hydration for the prevention of CI-AKI in patients with chronic kidney disease undergoing cardiac catheterization.

Methods This prospective randomized single-blind clinical trial enrolled 114 eligible patients with an estimated glomerular filtration rate (eGFR) of $15 < \text{eGFR} \leq 60$ mL/min/1.73 m^2 [according to the level-modified Modification of Diet in Renal Disease formula (MDRD)] and stable ischemic heart disease undergoing coronary procedures. The patients were randomly allocated 1:1 into the LVEDP-guided hydration group ($n = 57$) or the standard hydration group ($n = 57$). CI-AKI was defined as a greater than 25% or greater than 0.5 mg/dL (44.2 mmol/L) increase in the serum creatinine concentration compared with the baseline value. Hydration with 0.9% sodium chloride at a rate of 1 mL/kg/h (0.5 mL/kg/h if left ventricular ejection fraction < 40%) within 12 h was given to all the patients in both groups before the procedure. In the LVEDP-guided group, the hydration infusion rate was adjusted according to the LVEDP level during and after the procedure.

Results The incidence of CI-AKI was 7.01% (4/57) in the LVEDP-guided group vs 3.84% (2/52) in the standard hydration group (summary odds ratio 0.53, 95% CI 0.093–3.022; $P = 0.463$). Major adverse cardiac events, hemodialysis, or related deaths occurred in neither of the groups during hospitalization or the 30-day follow-up.

Conclusions In the present study, LVEDP-guided fluid administration, by comparison with standard hydration, failed to offer protection against the risk of CI-AKI in patients with renal insufficiency undergoing coronary angiography with or without percutaneous coronary intervention.

Keywords Left ventricular end-diastolic pressure · Stable ischemic heart disease · Chronic kidney disease · Contrast-induced acute kidney injury · Prevention

Introduction

Contrast-induced acute kidney injury (CI-AKI), also referred to as contrast-induced nephropathy (CIN]) [1], has become a serious post-percutaneous coronary intervention (PCI) complication which causes iatrogenic renal failure and is considered the third leading cause of AKI in hospitalized patients [2–4].

Different populations, along with a lack of a universal definition of CIN, has created a wide range (2–30%) of CI-AKI incidence across studies [5, 6]. Importantly, the incidence might reach 50% following coronary angiography

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(CAG) or PCI in high-risk patients [7, 8]. Generally, CI-AKI is reversible but causes prolonged hospitalization and higher health-care costs [2, 9–11], with an increase in long-term morbidity and mortality [6, 12, 13].

CI-AKI typically occurs within 72 h after iodinated contrast material administration, usually characterized by an increase in the serum creatinine (SeCr) concentration of more than 0.5 mg/dL (44 µmol/L) or by an increase of at least 25% from the baseline value [11].

There is no treatment for CIN and, consequently, prevention is an important strategy. Traditionally, the guidelines recommend prophylactic hydration for all patients undergoing CAG or PCI [14], which is generally based on expert consensus and its true benefit is poorly examined in a randomized controlled trial setting [4]. Interestingly, a recent trial even showed the non-inferiority of no prophylaxis vs hydration in a high-risk population undergoing elective coronary procedures, which underscores the need for more clarification on the matter [31]. In this regard, little evidence exists about a well-defined and, at the same time, cost–benefit protocol for the rate and duration of fluid administration [15–17]. Imprudent hydration may cause a wide range of complications (from phlebitis to pulmonary edema), which might complicate the patient's situation. Importantly, the conflicting results of recent trials on the efficacy of adjunctive therapies on CIN prevention (statin, *N*-acetylcysteine, sodium bicarbonate, etc.) have led to the acceptance of hydration as the central strategy for CIN prevention [18].

Left ventricular end-diastolic pressure (LVEDP)-guided intravascular volume expansion is a meticulous way of guiding fluid therapy in patients undergoing cardiac catheterization [19, 20]. The Prevention of Contrast Renal Injury with Different Hydration Strategies (POSEIDON) trial suggested that the LVEDP-guided intravenous administration of normal saline is well tolerated and could substantially reduce the incidence of CIN and major adverse clinical events in patients with combined chronic kidney disease and one or more several risk factors undergoing cardiac catheterization [19].

The purpose of the present trial was to investigative the efficacy of fluid administration guided by LVEDP as compared with standard hydration with normal saline in patients with chronic kidney disease undergoing diagnostic/therapeutic cardiac catheterization.

Methods

Study population

The study was a prospective randomized single-blind clinical trial. The study protocol was approved by the Ethics Committee of Rajaie Cardiovascular, Medical and Research Center (Tehran, Iran), and all the recruited patients signed an informed consent form before participating in the study.

Between April 2017 and July 2018, patients who were admitted for elective CAG or PCI at our institution were screened for eligibility.

The principal inclusion criteria included patients with stable ischemic heart disease over 18 years old scheduled for diagnostic cardiac angiography or PCI and an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m^2 or lower [according to the level-modified Modification of Diet in Renal Disease formula (MDRD)]. The principal exclusion criteria included emergent cardiac catheterization, exposure to radiographic contrast media within 3 days prior to recruitment, candidacy for renal replacement therapy or eGFR < 15 mL/min/1.73 m^2, acute decompensated heart failure or recent pulmonary edema, cardiogenic shock, hypotension (systolic blood pressure < 90 mmHg), severe valvular heart disease, history of renal or heart transplantation, recent change of more than 15% in the eGFR within 2 days prior to recruitment, allergy to contrast agents, electrolyte imbalance, malignant neoplasms, severe infection, mechanical aortic prostheses, left ventricular thrombosis, aortic balloon counter-pulsation treatment, and pregnancy.

Study protocol

The eligible patients were randomized using computer-generated random numbers in a 1:1 fashion to either LVEDP-guided therapy or standard fluid administration (control group), and concealment was performed via sealed envelopes containing the assigned groups. In both groups, patients on metformin have stopped their medication and during the first 48-h after the procedure. Metformin should be restarted only if the creatinine value was stable at the 72-h test.

An infusion of isotonic saline at a rate of 1 mL/kg/h (0.5 mL/kg/h if left ventricular ejection fraction < 40%) within 12 h was administered to all the patients before and during the procedure.

The patients, data collectors, outcome adjudicators, and data analysts were blinded to the group assignment. CAG or PCI was performed based on the standard protocols. LVEDP was measured before the administration of contrast media with an angled 5-F pigtail catheter in all the participants. Thereafter, the patients were randomly assigned to either the LVEDP-guided or the standard hydration group.

The hydration rate was adjusted according to LVEDP for 4 h following the procedure in the LVEDP-guided group as follows: 5 mL/kg/h for LVEDP of lower than 13 mmHg, 3 mL/kg/h for LVEDP of 13–18 mmHg, and 1.5 mL/kg/h for LVEDP of higher than 18 mmHg. Standard hydration was continued for the control group at a rate of 1 mL/kg/h (0.5 mL/kg/h if left ventricular ejection

fraction < 40%) within 12 h after the procedure. In all the patients, blood samples were collected at admission and at 24 and 72 h after the procedure to measure the levels of blood urea nitrogen (BUN) and SeCr. The volume of the consumed contrast material, the ratio of the contrast medium volume (CMV) to creatinine clearance (CMV/eGFR ≥ 3.7 was defined as a significant and independent predictor of an early abnormal increase in SeCr), and the patients' demographic information—including age, sex, weight, drug history, history of diabetes mellitus (DM), and hypertension—were recorded in data-collection forms.

End-point outcomes

The primary end point of the study was the incidence of CI-AKI, defined as an increase in the SeCr concentration of more than 0.5 mg/dL (44 μmol/L) or as an increase of at least 25% from the baseline value 24 or 72 h after the contrast medium infusion.

The secondary end points were changes in SeCr and BUN within 24 or 72 h, the relationship between CI-AKI and the CMV, and major adverse cardiac events (including all-cause mortality, renal replacement therapy, acute heart failure, pulmonary edema, and cerebrovascular events) occurring during hospitalization and within the 30-day follow-up period.

Statistical analysis

Sample size calculation

Based on a study by Brar et al. [19], the incidence of CI-AKI was reported to be 6.7% and 26.3% in the LVEDP-guided group and the standard fluid administration protocol, respectively. With an 80% power ($\alpha = 0.05$) and 95% confidence interval (95% CI), 57 patients in each group were needed to show a significant result.

All the statistical analyses were performed using SPSS software, version 23.0, (SPSS, Inc, Chicago, IL, USA). All the tests were two-tailed, and the differences were reported as significant if the P value was less than 0.05. The Kolmogorov–Smirnov test was applied to evaluate the normal distribution of the data. The normally distributed continuous data, expressed as the mean ± the standard deviation (SD), were analyzed using the Student's t test, the χ^2 test, or the Fisher exact test. The continuous variables were compared between the two groups and in each group before and after the intervention using the independent t test and the paired sample t test, correspondingly. Additionally, the generalized estimating equation (GEE) was used for the longitudinal data.

Results

Demographic and clinical data

A total of 114 patients (mean age: 67 ± 8 years, 72 men) were randomly assigned to the intervention group ($n = 57$) and the control group ($n = 57$). Five patients in the control group were lost to follow-up, and 109 patients (LVEDP-guided group = 57, standard hydration group = 52) were included in the final analysis (Fig. 1).

The overall prevalence of hypertension (blood pressure > 140/90 mmHg or treatment with antihypertensive medication) and DM was 66.97% and 36.69%, respectively. The study population's demographic and medication characteristics are listed in Table 1. No significant differences were found between the two groups regarding age, sex, the body mass index (kg/m^2), history of DM and hypertension, baseline LVEDP and eGFR, and medication history except for angiotensin-converting enzyme inhibitors, contrast volume and the rate of PCI (Table 1).

Incidence of CIN and multiple logistic regression analysis

The overall incidence of CI-AKI for the enrolled high-risk patients was 5.50% (6/109):7.01% (4/57) in the LVEDP-guided group vs 3.84% (2/52) in the control group. There was no significant difference in the incidence of CI-AKI [summary odds ratio (OR) 0.53, 95% CI 0.093–3.022; $P = 0.463$] when the LVEDP-guided group was compared with the standard hydration group. There were no significant differences in medication history for angiotensin-converting enzyme inhibitors, contrast volume and the rate of PCI in patients with and without CI-AKI (Table 2).

The relationship between CI-AKI and subgroup, defined by the CMV, was analyzed. The proportion of the patients with CI-AKI was lower but not significant in the group with the CMV/eGFR of less than 3.7 than in the group with the CMV/eGFR of equal to or greater than 3.7 (2.9% vs 9.8%; $P = 0.131$). There was no significant difference even when including the medication history for angiotensin-converting enzyme inhibitors and PCI as covariates ($P = 0.794$ by Binary logistic regression).

Changes in BUN and SeCr

At baseline, there were no significant differences in BUN and SeCr between the LVEDP-guided group and the control group (Table 1). In both the LVEDP-guided group and the control group at 24 h after the procedure, BUN decreased significantly compared with the baseline value ($P = 0.022$

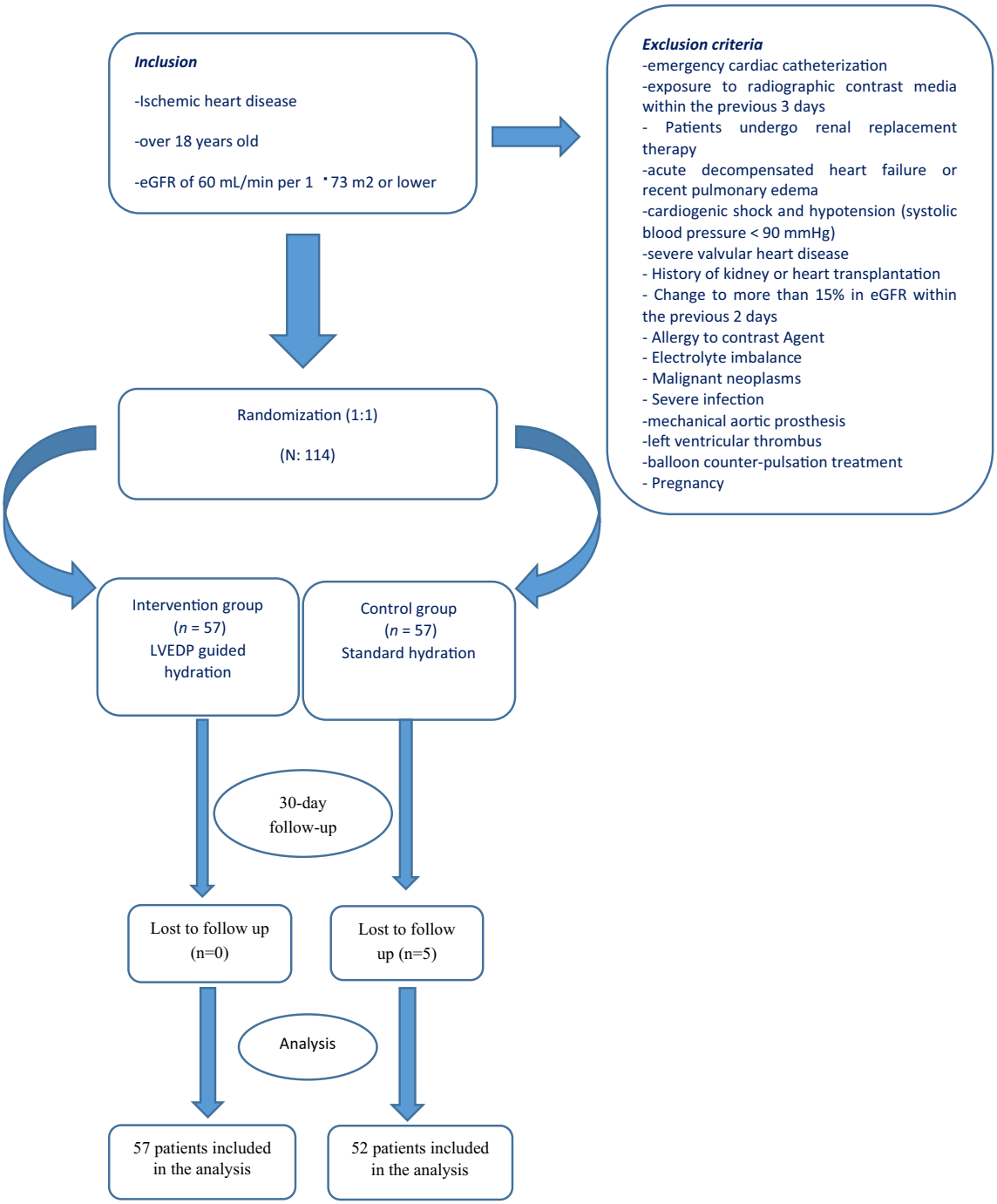

Fig. 1 Consort flow chart

and $P = 0.008$, respectively); however, at 72 h postprocedurally, a nonsignificant increase and decrease in the BUN level were detected in the LVEDP-guided group and the control group, correspondingly (Table 3).

A decrement in the SeCr level was observed after the procedure in the LVEDP-guided group, which was significant only during the first 24 h ($P < 0.001$) (Table 3). On the other hand, in the control group, SeCr decreased significantly compared with the baseline value in both 24- and 72-h time intervals ($P < 0.001$ and $P = 0.004$, respectively) (Table 3). The BUN and SeCr levels were both lower at 24 and 72 h following the procedure in the control group compared with the LVEDP-guided group; the changes were significant at 72 h ($P = 0.008$ and $P = 0.011$, respectively), but they were not statistically significant at 24 h ($P = 0.178$ and $P = 0.065$, correspondingly) (Fig. 2).

Table 1 Baseline characteristics of the study groups

Variable	LVEDP-guided group ($n=57$)	Standard hydration group ($n=52$)	*P* value
Age (years)[a]	67.19 ± 8.87	67.07 ± 8.73	0.945
Sex (male)[b]	39 (68.42)	33 (63.46)	0.585
BMI[a]	23.08 ± 2.30	22.32 ± 1.90	0.064
HTN[b]	39 (68.42)	34 (65.38)	0.736
DM[b]	22 (38.59)	18 (34.61)	0.667
Metformin[b]	9 (15.78)	9 (17.30)	0.831
Furosemide[b]	8 (14.03)	9 (17.30)	0.638
ARB[b]	23 (40.35)	16 (30.76)	0.297
ACEI[b]	20 (35.08)	9 (17.30)	0.036
Statin[b]	29 (50.87)	29 (55.76)	0.609
BUN (mg/dL)[a]	26.29 ± 12.64	23.86 ± 8.06	0.239
SeCr (mg/dL)[a]	1.38 ± 0.383	1.28 ± 0.197	0.078
Baseline GFR (mL/min/1.73 m^2)[a]	50.07 ± 9.58	48.51 ± 8.18	0.368
Baseline LVEDP (mmHg)[a]	15.36 ± 5.01	14.92 ± 4.56	0.630
Contrast volume (cc)[a]	140.25 ± 81.01	193.92 ± 104.88	0.003
PCI[b]	19 (33.33)	27 (51.92)	0.050

ACEI angiotensin-converting-enzyme inhibitor, *ARB* angiotensin receptor blocker, *BMI* body mass index, *BUN* blood urea nitrogen, *DM* diabetes mellitus, *GFR* glomerular filtration rate, *HTN* hypertension, *LVEDP* left ventricular end-diastolic pressure, *SeCr* serum creatinine

[a]Mean ± SD

[b]*N* (%)

Table 2 Comparison of medication history for ACEI, PCI and contrast volume in patients with and without CI-AKI

Variable	With CI-AKI ($n=6$)	Without CI-AKI ($n=103$)	*P* value
ACEI[a]	1 (16.66)	28 (27.18)	0.575
PCI[a]	2 (33.33)	44 (42.71)	0.655
Contrast volume (ml)[b]	200.33 ± 68.35	163.84 ± 97.81	0.371

[a]*N* (%)

[b]Mean ± SD

Major adverse cardiac events during the in-hospital stay and the 30-day follow-up period

During the hospitalization and the 30-day follow-up, no major adverse cardiac events (cardiac death, nonfatal myocardial infarction, acute decompensated heart failure, etc.) were recorded in either of the groups. Importantly, all the encountered cases of CIN were managed conservatively, and no renal replacement therapy was reported during the hospitalization or the follow-up.

Table 3 Comparisons of the BUN and SeCr levels between the baseline and 24 h and 72 h after the procedure in both study groups

Group	Baseline	24 h	72 h	*P* value*	*P* value$^+$
BUN (mg/dL) level in the LVEDP-guided group	26.29 ± 12.64	23.80 ± 10.93	27.56 ± 12.53	0.022	0.166
BUN (mg/dL) level in the standard hydration group	23.86 ± 8.065	21.46 ± 6.27	22.26 ± 6.90	0.008	0.208
SeCr (mg/dL) level in the LVEDP-guided group	1.38 ± 0.383	1.271 ± 0.393	1.35 ± 0.403	< 0.001	0.307
SeCr (mg/dL) level in the standard hydration group	1.28 ± 0.197	1.159 ± 0.191	1.198 ± 0.197	< 0.001	0.004

Indicated as mean ± SD

BUN blood urea nitrogen, *DM* diabetes mellitus, *LVEDP* left ventricular end-diastolic pressure, *SeCr* serum creatinine

**P* value from the comparison between the baseline and 24 h after the procedure, $^+$*P* value from the comparison between the baseline and 72 h after the procedure

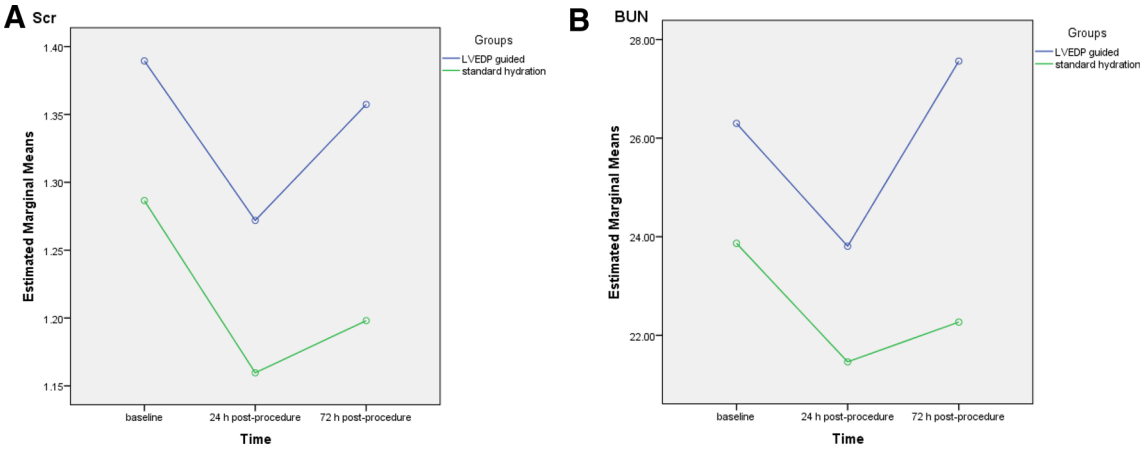

Fig. 2 Profile plots for the BUN and SeCr levels between the 2 groups at the 3 study time points (baseline and 24 h and 72 h after the procedure). SeCr (**a**) and BUN (**b**) levels were both lower at 24 h and 72 h after the procedure in the control group compared with the LVEDP-guided group. *SeCr* serum creatinine, *BUN* blood urea nitrogen, *LVEDP* left ventricular end-diastolic pressure

Discussion

In the present prospective randomized single-blind clinical trial, we sought to assess the superiority of the LVEDP-guided fluid administration strategy over the standard hydration approach for the prevention of CI-AKI in a high-risk population undergoing diagnostic and therapeutic procedures. Mainly, we found that the use of the LVEDP-guided hydration strategy, compared with standard hydration, failed to confer a decreased risk of CI-AKI.

Despite its low incidence, CI-AKI is considered a serious post-coronary intervention complication and the third leading cause of AKI in hospitalized patients [2, 4]. CI-AKI is generally reversible at the expense of a more prolonged hospitalization and higher health-care costs [2, 9–11]. Importantly, in a small but considerable number of patients, the renal condition might deteriorate, resulting in renal replacement therapy and increased in-hospital mortality [9–11]. Further, 13% of those requiring in-hospital dialysis might need the treatment permanently, which increases the mortality rate by about fivefold that in patients who do not develop CI-AKI [6, 12, 13, 21–23]. In addition, the risk of CI-AKI in intra-arterial contrast administration is at least twofold that of intravenous administration, which places patients undergoing coronary intervention at a higher risk [24, 25].

The pathophysiology of CIN involves a complex interaction of several mechanisms which is still not fully understood [26]. Direct cytotoxic effects through acute sustained vasoconstriction, altered renal hemodynamics, auto- and paracrine factors, regional hypoxia, and direct tubular and vascular endothelial injury with reactive oxygen species (ROS) have all been propounded as the mechanisms underlying CI-AKI [24, 26–29]. Chronic kidney disease (eGFR < 60 mL/min/1.73 m^2), resulting in a reduced number of nephrons, is deemed an important predictor of CI-AKI [24, 27].

There are no available options for treating CI-AKI and, consequently, prevention is the central strategy. Although various adjunctive therapies have been introduced to prevent the risk of CIN, the mixed results of recent investigations have considerably dampened the initial enthusiasm for the use of such strategies and placed hydration therapy back in the spotlight [18]. The international guidelines, which are mainly based on expert consensus, recommend prophylactic fluid administration for 6–12 h before and after the administration of the contrast medium for all patients as the main preventive strategy [14, 15, 30]. Expanding the plasma volume with normal saline administration might alleviate CI-AKI by reducing ROS, diluting the contrast medium, and diminishing renin activation [28, 31]. However, the true clinical value of hydration therapy has been scarcely studied in a proper setting. There is even a recent investigation, the AMACING trial [Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING)], which reported that no prophylaxis strategy tends to be non-inferior and cost-saving in preventing CIN among high-risk patients with an eGFR of 30–59 mL/min/1.73 m^2 [32]. The observation has been even approved by a recent meta-analysis performed by Jiang et al. [4], who indicated that no prophylactic hydration is non-inferior to intravenous hydration in terms of the incidence of CI-AKI in patients with a baseline eGFR ranging from 30 to 60 mL/min/1.73 m^2. Despite this recent conflicting evidence, the periprocedural hydration strategy is widely applied in patients undergoing various diagnostic and therapeutic settings, imposing a significant burden on health-care systems with regard to both lengths of stay and hospital costs [9–11].

In addition, there is no general agreement on the rate and amount of hydration therapy before and after the procedure.

Optimal fluid administration regimens should be based on adjusting volumes according to the patient's hydration status. Patients' intravascular volume status can be assessed via hemodynamic monitoring, which may be a good index for guidance on the rate of fluid administration [33, 34]. Periprocedural infusion of fluids based on individual hemodynamic parameters such as central venous pressure, left LVEDP, and urinary flow, as well as the application of bio-impedance vector analysis, has been implicated as the strategy for decreasing the incidence of CI-AKI in high-risk patients [17, 19, 20, 35, 36].

Brar et al. [19] were the first to test the value of LVEDP-guided fluid therapy in patients undergoing diagnostic cardiac catheterization. In the POSEIDON randomized controlled trial, CI-AKI occurred less frequently in the LVEDP-guided group than in the control group [6.7% (12/178) vs 16.3% (28/172); relative risk 0.41, 95% CI 0.22–0.79; $P=0.005$] and the authors concluded that the intravenous administration of normal saline, guided by LVEDP, is well tolerated and can substantially reduce the incidence of CI-AKI and major adverse clinical events in patients undergoing cardiac catheterization [19]. In contrast, we found that LVEDP-guided hydration could not reduce the incidence of CI-AKI in our patients with renal insufficiency undergoing CAG with or without PCI. The incidence of CI-AKI was 7.01% (4/57) in our LVEDP-guided group vs 3.84% (2/52) in our control group (summary OR 0.53, 95% CI 0.093–3.022; $P=0.463$). The discrepancy between these two studies may be explained by the differences in the studied populations and the duration of hydration therapy in the control group of each trial. The POSEIDON study's inclusion criteria included an eGFR of 60 mL/min/1.73 m^2 or lower; age 18 years or older; and at least one of the following: DM, history of congestive heart failure, hypertension (blood pressure > 140/90 mmHg or treatment with antihypertensive medication), or age older than 75 years. The patients in the POSEIDON study had a high prevalence of hypertension and DM by comparison with the participants in the present study (98% and 51% vs 66.97% and 36.69%, respectively).

Moreover, in the current study, standard hydration in the control group was continued for 12 h after the procedure, which is in contrast with the POSEIDON study, in which it was discontinued after 4 h [19].

The ratio of the CMV to a minimum creatinine clearance level of 3.7 is a significant and independent predictor of an early abnormal increase in SeCr [37, 38]. In our study, the proportion of the patients with CI-AKI was lower in the group with the CMV/eGFR of less than 3.7 than in the group with the CMV/eGFR of equal to or greater than 3.7 (2.9% vs 9.8%; $P=0.131$).

Some limitations in the present study should be considered. First, our study was a single-center trial with a limited sample size. Second, the study excluded patients with emergency cardiac catheterization, acute decompensated heart failure or recent pulmonary edema, cardiogenic shock, hypotension (systolic blood pressure < 90 mmHg), and severe valvular heart disease, who are considered to be at the highest risk for developing CIN. Finally, the rate of PCI, ACE administration and contrast volume were unbalanced between our two studied groups. Although those factors have no significant confounding effect in our analysis, they might potentially influence the results.

In conclusion, this study indicates that LVEDP-guided hydration, in comparison with standard hydration therapy, cannot reduce the risk of CIN in patients with chronic kidney disease undergoing coronary procedures.

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Compliance with ethical standards

Conflict of interest There are no conflicts of interest.

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