Prevention of Contrast-induced Nephropathy With Oxygen Supplementation

A Randomized Controlled Trial

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Introduction. The aim of the study was to investigate the efficacy of nasal oxygen as a supplementation to hydration therapy in reducing the risk of developing contrast-induced nephropathy (CIN).
Materials and Methods. In a randomized controlled trial, 348 patients scheduled to undergo elective coronary angiography were randomly allocated to standard hydration plus 2 L/min to 3 L/min nasal oxygen (from 10 minutes before the procedure until the end of the procedure) (n = 176) or standard hydration alone (n = 176). The primary outcome measure was development of CIN defined as either an increase of 25% or more in serum creatinine concentrations or an increment of at least 0.5 mg/dL in serum creatinine concentrations 48 hours after catheterization.
Results. Of the 348 patients who completed the study, 105 developed CIN (30.2%; 95% confidence interval, 25.4% to 35.0%). A diagnosis of CIN was made in 32 (18.6%) and 73 (41.5%) patients in the nasal oxygen and control arms, respectively ($P < .001$). In the intervention arm, creatinine concentrations postcontrast remained relatively constant (average change, 2.7%), whereas a significant increase of 17.3% was recorded in the control arm ($P < .001$; effect size, 11.8%).
Conclusions. Supplementation with nasal oxygen in addition to standard hydration appears to be an effective strategy in reducing CIN. The effect size for this intervention seems to be moderate.

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INTRODUCTION

Contrast-induced nephropathy (CIN) is a leading cause of iatrogenic acute kidney injury and is believed to be responsible for about 11.5% of cases of acute in-hospital kidney failure.[1] In the majority of cases, the loss in kidney function following CIN is reversible, and the incidence of life-threatening failure requiring renal replacement therapy appears to be extremely low (around 0.06%).[2] Of importance, however, is the fact that developing CIN is strongly associated with long-term risk of mortality. In a retrospective assessment of 7586 patients, it was shown that the 5-year mortality rate in CIN patients is 3 times as high as those not developing CIN after adjustment for other risk factors.[3]

Certain underlying factors contribute to an increased probability of developing CIN. A useful classification for CIN risk factors is to sketch them into 2 broad categories of modifiable and nonmodifiable. Among nonmodifiable risk factors, pre-existing kidney failure seems to be the most crucial.[4] Other risk factors in this category are advanced age, diabetes mellitus, and congestive

heart failure or decreased ejection fraction.[4] Modifiable risk factors the correction of which is the target for CIN prevention strategies include the use of nephrotoxic medications, use of diuretics, use of renin-angiotensin-aldosterone inhibitors, anemia, hypotension, dehydration, administering large doses of contrast media, and use of high-osmolality agents. In most of modifiable and also nonmodifiable risk factors, end-organ hypo-oxygenation, secondary to impaired perfusion to the kidneys, appears to be a shared feature. Inadequate perfusion, by depleting renal anti-oxidant capacity, hampers the kidney's ability to negate the effects of contrast-induced oxidative stress.

Volume expansion strategies aimed at improving renal perfusion and oxygenation prior to and after the administration of contrast media have yielded promising results, and have been endorsed by clinical practice guidelines.[5-9] Recently, it has been suggested that addition of oxygen supplementation to hydration using 0.9% normal saline could result in further reduction of CIN compared with hydration alone.[10] The idea of reducing the risk of CIN using oxygen supplementation appears worthwhile since it is readily available, is easily administered, and carries virtually no potential risks to the patient. The present randomized controlled trial was thus designed to investigate the effectiveness of oxygen supplementation in reducing incident CIN in patients receiving contrast media.

MATERIALS AND METHODS

Design and Intervention

In order to evaluate the efficacy of oxygen administration on the risk of developing CIN, a single-center, parallel-group, randomized clinical trial was planned. Using a randomization module in Microsoft Excel, qualified patients were assigned to the control or intervention arms of the trial. In addition to standard care, patients in the intervention arm received oxygen via a nasal cannula at the rate of 2 L/min to 3 L/min beginning 10 minutes before the procedure until the end of the procedure. For patients in the control arm, standard care was offered. All of the patients received normal saline at the dose of 1 mL/kg/h, 12 hours leading to the procedure and 12 hours after the procedure. Diuretics were discontinued 24 hours prior to the procedure, if applicable. For all of the patients, the same low-osmolality nonionic contrast media, Iopromide (Ultravist, Bayer, Germany) was administered. Randomization of patients was performed by the principal investigator. The attending cardiologist conducting the procedure and the nursing personnel caring for the patient were not involved in intervention allocation. No sham intervention for controls was performed. The hospital laboratory conducting the laboratory assessments before and after the procedure was blinded to the allocation status of the patients. The trial protocol was registered at the Iranian Registry of Clinical Trials (Registration No, IRCT2014082618936N1).

Patients

Between September and December 2014, all patients scheduled to undergo elective coronary angiography or angioplasty in the Catheterization Laboratory of Shahid Rajai Hospital (a tertiary heart center affiliated with Tehran University of Medical Sciences) were assessed for eligibility. Patients were deemed eligible if they were at least 35 years old and had no exclusion criteria. The exclusion criteria were as follows: (1) baseline serum creatinine concentrations greater than 1.5 mg/dL, (2) need for emergency catheterization, (3) receiving contrast media for diagnostic or therapeutic interventions in the past 3 months, (4) uncontrolled congestive heart failure, (5) uncontrolled chronic obstructive pulmonary disease, (6) history of allergy to contrast media, and (7) pregnancy or lactation. Written informed consent was obtained from all enrolled participants. All procedures dealing with human subjects were conducted in accordance with the latest revision of the Helsinki Declaration. The Ethics Committee of Tehran University of Medical Sciences approved the trial protocol.

Assessment and Outcomes

A detailed medical history was obtained and routine physical examination was performed. A venous blood sample was obtained from each participants prior to the procedure and was sent to hospital laboratory. An arterial sample was also drawn from the radial artery directly into preheparinized containers and was immediately sent to the laboratory for measurement of partial pressure of oxygen (PO_2). For patients in the intervention arm, a repeat arterial sampling was done using the same protocol at the end of the

catheterization and before going to the recovery room. A second venous sample was drawn from all of the patients 48 hours after administration of contrast medium. Serum creatinine concentrations were determined using the Jaffe method. Estimated glomerular filtration rate (GFR) was calculated using the Chronic Kidney Disease-Epidemiology Collaboration formula.[11] The primary outcome measure of interest was development of CIN defined as either an increase of 25% or more in serum creatinine concentrations, or an increment of at least 0.5 mg/dL in serum creatinine concentrations 48 hours after catheterization. The other primary outcome was change in the mean serum creatinine concentrations 48 hours after administration of contrast medium (postcontrast) irrespective of the incident CIN.

Statistical Analysis

All statistical analyses were conducted using the SPSS software (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation, if normally distributed and as median (interquartile range) if not normally distributed. Categorical variables were described as proportions (percentages). Baseline continuous variables across trial arms were compared using the independent *t* test or the Mann-Whitney U test, where appropriate. The distribution of categorical variables between the intervention and control arms of the trial where compared using the chi-square test or the Fisher exact test where appropriate. Changes in serum creatinine concentrations 48 hour postcontrast, between the two groups were investigated using the analysis of covariance, adjusting for baseline creatinine concentrations. In this model, the effect size was determined by partial eta squared and was expressed in percentages. Based on Cohen recommendations, a partial eta squared value of around 1% indicates small effect, 6% medium effect, and 13.8% or above large effect. To evaluate the relationship between changes in PO_2 and changes in creatinine concentrations, the correlation test was done and the Pearson product moment correlation coefficient was calculated. Multivariable logistic regression was used to assess the association of various risk factors and also the intervention with the development of CIN. For each risk factor, and also for the intervention, the odds ratio (OR) and the 95% confidence interval (CI) were determined. Finally, we sought to investigate the efficacy of the intervention by patient subgroups (eg, men and women). For this purpose, the data was stratified and the chi-square (of the Fisher exact) was used to test the difference in CIN frequency within each stratum. In all of the tests, a *P* value less than .05 was considered significant.

RESULTS

The flow diagram of the clinical trial, delineating the number of patients assessed for eligibility, randomized, and analyzed is shown in Figure 1. Three hundred and forty-eight patients were included in the final analysis (172 in the nasal oxygen arm and 176 controls). Comparisons of demographic and clinical variables between the two arms of the trial are presented in Table 1. The mean age of the participants were similar between the two groups. An age greater than 55 years was not a risk factor for CIN. Male-female ratio did not significantly differ between the trial arms. Frequency of diabetes mellitus, the mean percentage of ejection fraction, baseline PO_2, baseline serum creatinine, and the median volume of contrast media used were also comparable across trial arms.

Overall, 105 patients developed CIN, giving rise to a prevalence rate of 30.2% (95% CI, 25.4% to 35.0%). Thirty-three patients met both criteria of rise of serum creatinine of at least 25% and absolute increment of 0.5 mg/dL or more. In the remaining 72 patients with CIN, 67 only met the former, while 8 were diagnosed using the latter criterion. A diagnosis of CIN was made in 32 (18.6%) and 73 (41.5%) patients in the nasal oxygen and control arms, respectively. The patients not receiving nasal oxygen were 123% more likely to develop CIN after the intervention ($P < .001$). With respect to the other primary outcome, change in mean creatinine concentrations, a significant between-group difference was also noted and the findings are demonstrated in Figure 2. In the intervention arm, after 48 hours, creatinine concentrations remained relatively constant (average change, 2.7%), whereas a significant increase of 17.3% in the control arm was recorded ($P < .001$). The calculated effect size was 11.8%, suggesting a moderate effect for using nasal oxygen in cushioning creatinine levels and preventing CIN.

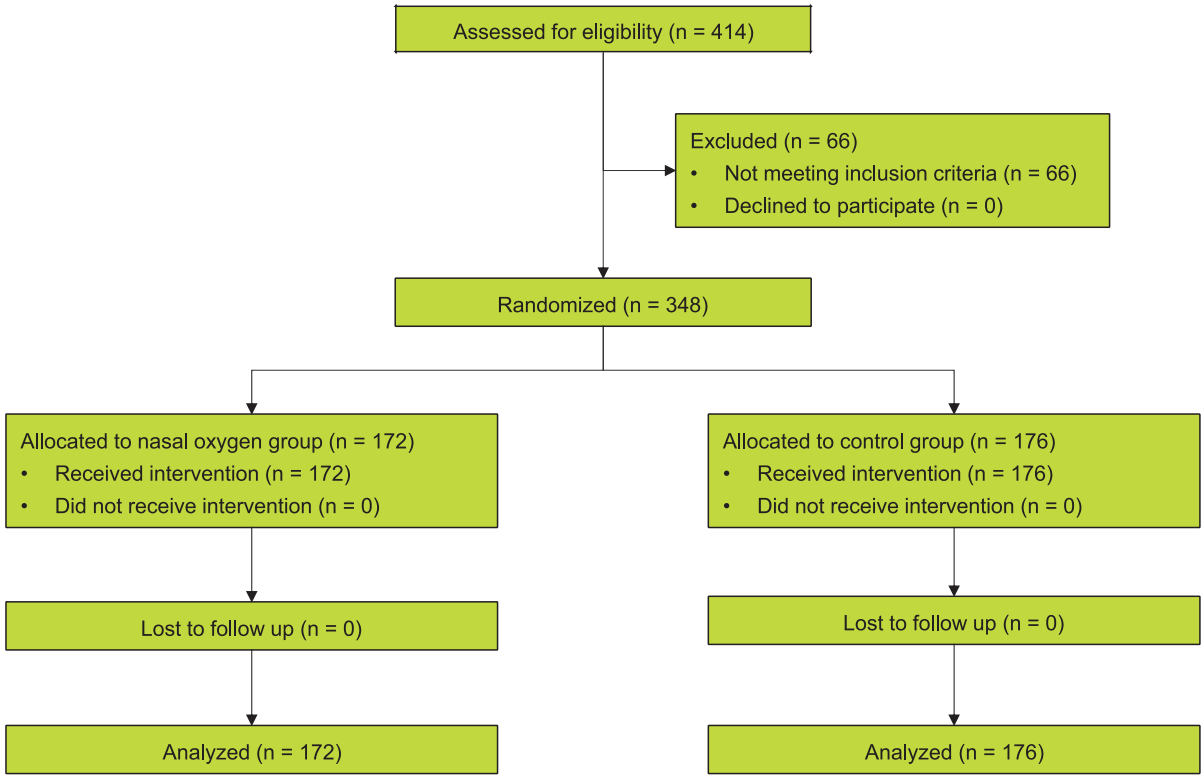

Figure 1. Flowchart of the patients assessed for eligibility, enrolled, randomized, and analyzed.

Within-group analysis of the nasal oxygen arm showed that administration of oxygen significantly increased PO_2 (75.9 mm Hg versus 118.2 mm Hg, $P < .001$). Furthermore, this increment in PO_2 was significantly and negatively correlated with changes in creatinine concentrations 48 hours after the intervention, indicating that short-term increase in arterial partial PO_2 was associated with decreased creatinine concentration afterwards (Figure 3).

Multivariable logistic regression model was used to investigate the association of risk factors and also the intervention on the risk of developing CIN and the results are shown in Table 2. Male sex, having diabetes mellitus, diminished ejection fraction, and chronic kidney disease defined as an estimated GFR less than 60 mL/min/1.73 m^2, were significantly associated with incident CIN. The largest OR was attributed to having diabetes mellitus followed by male sex. An increased risk of developing CIN with older age, low PO_2 at baseline, and use of high volumes of contrast media was also noted, albeit not reaching statistical significance.

Table 1. Baseline Characteristics of Participants*

Characteristic	Trial Arm		*P*
	Nasal Oxygen (n = 172)	Control (n = 176)	
Age, y	58.8 ± 11.7	57.8 ± 10.8	.43
Sex			
Female	64 (37.2)	57 (32.4)	
Male	108 (62.8)	119 (67.6)	.37
History of diabetes	52 (30.2)	43 (24.4)	.23
Ejection fraction, %	48.7 ± 8.7	49.3 ± 6.5	.66
Pressure of oxygen, mm Hg	75.9 ± 8.4	75.2 ± 9.4	.49
Serum creatinine, mg/dL	0.96 ± 0.24	0.93 ± 0.15	.22
Contrast volume, mL	200 (100 to 250)	150 (100 to 257)	.33

*Values are frequencies (percentage) for categorical variables and mean ± standard deviation for continuous variables except for contrast volume, which is median (interquartile range).

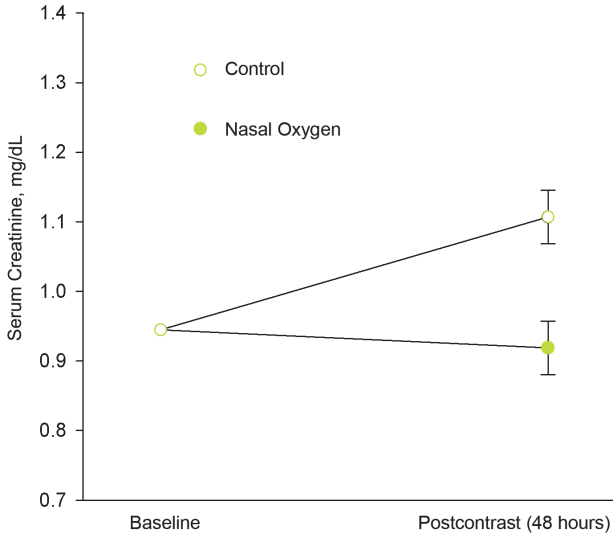

Figure 2. Efficacy of nasal oxygen in changing mean serum creatinine concentrations postcontrast.

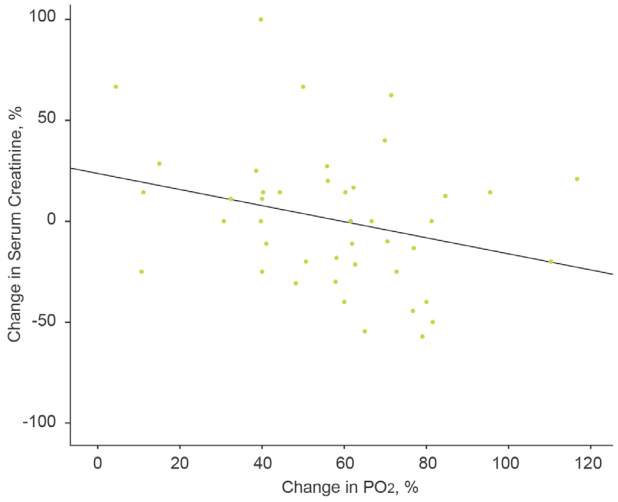

Figure 3. Correlation of changes in pressure of oxygen (PO_2) with changes in serum creatinine concentrations postcontrast in the intervention arm (r = -0.0286, *P* < .001).

Multivariable regression analysis also revealed that nasal oxygen administration significantly reduced the risk of CIN (OR, 0.25; 95% CI, 0.15 to 0.44; *P* < .001) independent of other underlying risk factors (Table 2).

We further investigated the effect of associated risk factors for CIN on treatment efficacy and the findings are demonstrated in Table 3. The between-arm difference in the frequency of CIN was not significantly different among male patients, those with an ejection fraction less than 40%, those with a GFR less than 60 mL/min/1.73 m^2, and patients receiving more than 200 mL of contrast media. These findings indicated that the effectiveness of nasal oxygen administration might be less pronounced in certain high-risk groups of the patients.

DISCUSSION

The main finding of the present randomized controlled trial was that oxygen supplementation results in a significant reduction of incident CIN. While 41.5% of the patients in the control arm developed CIN, in the intervention arm, a markedly lower frequency rate of 18.6% was recorded. Analyzing serum creatinine concentrations as a continuous variable, this finding was confirmed that in the oxygen arm, post-contrast creatinine levels were comparable with baseline values, whereas patients in the control arm experienced an average increment of 17.3% in creatinine concentrations. Our findings are in agreement with 2 other clinical trials in this regard. In the first study by Sekiguchi and colleagues, 349 patients undergoing elective coronary angiography or percutaneous coronary intervention were randomly assigned to either oxygen (at the rate of 2 L/min using a nasal cannula) plus hydration or hydration alone. Based on their observation, the frequency of the main endpoint, defined as incident CIN 48 hours postprocedure, was significantly lower in the intervention compared

Table 2. Multivariate Logistic Regression Analysis for Prediction of Incident Contrast-induced Nephropathy

Factor	Odds Ratio (95% Confidence Interval)	*P*
Age ≥ 55 years	1.59 (0.87 to 2.89)	.13
Male sex	3.64 (1.94 to 6.84)	< .001
Positive history of diabetes	3.73 (2.05 to 6.80)	< .001
Ejection fraction ≤ 40%	2.11 (1.06 to 4.17)	.03
Baseline pressure of oxygen < 80 mm Hg	1.54 (0.87 to 2.70)	.14
Baseline glomerular filtration rate < 60 ml/min/1.73 m^2	2.26 (1.26 to 4.06)	.006
Contrast volume > 200 mL	1.25 (0.72 to 2.16)	.43
Intervention (nasal oxygen)	0.25 (0.15 to 0.44)	< .001

Table 3. Frequency of Contrast-induced Nephropathy by Subgroups

Subgroups	Contrast-induced Nephropathy (%)		*P*
	Nasal Oxygen (n = 172)	Control (n = 176)	
Age, y			
≥ 55 (n = 227)	24 (23.1)	52 (42.3)	.001
< 55 (n = 121)	8 (11.8)	21 (39.6)	.003
Sex			
Female (n = 121)	4 (6.3)	14 (24.6)	< .001
Male (n = 227)	28 (25.9)	59 (49.6)	.38
History of diabetes			
Yes (n = 95)	12 (23.1)	28 (65.1)	< .001
No (n = 253)	20 (16.7)	45 (33.8)	.002
Ejection fraction, %			
≤ 40 (n = 60)	11 (31.4)	13 (52.0)	.12
> 40 (n = 288)	21 (15.3)	60 (39.7)	< .001
Baseline pressure of oxygen, mm Hg			
< 80 (n = 120)	12 (18.8)	28 (50.0)	< .001
≥ 80 (n = 228)	20 (18.5)	45 (37.5)	.002
Baseline glomerular filtration rate, mL/min/ 1.73 m^2			
< 60 (n = 88)	17 (36.2)	20 (48.8)	.28
≥ 60 (n = 260)	15 (12.0)	53 (39.3)	< .001
Contrast volume, mL			
> 200 (n = 104)	12 (27.3)	24 (40.0)	.21
≤ 200 (n = 244)	20 (15.6)	49 (42.2)	< .001

with the control arm (0.6% versus 5.1%).[10] The authors also showed that in multivariable logistic regression analysis, an estimated GFR less than 60 mL/min/1.73 m^2 and a PO_2 less than 100 mm Hg were significantly associated with CIN.[10] Herein, we also showed that when placed in multivariable analysis, male sex, diabetes mellitus, an ejection fraction less than 40%, and also diminished GFR significantly predicted CIN occurrence. On the other hand, the administration of nasal oxygen emerged as a protective factor and patients in the nasal oxygen arm were about 4 times less likely to develop CIN compared with their counterparts in the control group. In the second clinical trial in 2014, the same research group demonstrated that oxygen preconditioning lowered the risk of CIN in a subgroup of patients with pre-existing chronic kidney disease defined as a GFR less than 60 mL/min/1.73m^2.[12]

While both of the trial by Sekiguchi and colleagues[10] and our trial suggest that oxygen supplementation lowers the risk of developing CIN, interpretation of findings should be made with caution and 2 corollary points need to be considered. First, analysis of serum creatinine concentrations demonstrated a clear advantage for nasal oxygen in reducing postcontrast creatinine concentrations; however, the observed effect size for between-group difference was 11.8%, which is considered moderate. Therefore, while oxygen supplementation is an effective and safe strategy for reducing the risk of CIN, its efficacy appears to be moderate and should be viewed in this context. Second, based on multivariable regression analysis, male sex, diabetes mellitus, an ejection fraction less than 40%, and a GFR less than 60 mL/min/1.73 m^2 were the main risk factors for developing CIN. To investigate whether the efficacy of the intervention differs in certain high-risk populations for CIN, we conducted a subgroup analysis. Subgroup analysis revealed that while nasal oxygen reduces CIN in females, the between-arm difference in male patients is not statistically significant. Similar findings were also observed for diminished ejection fraction, and diminished GFR. On the other hand, stratifying patients by diabetes status revealed no discrepancies with regard to effectiveness of the intervention. Taking these observations into account, it could be argued that certain high-risk patients might not receive the same level of benefits from this intervention as to that of the low-risk patients. Future randomized trials with larger sample sizes that are specifically designed to evaluate the efficacy of nasal oxygen

in high-risk patients are thus paramount.

In the intervention arm of this trial, administration of nasal oxygen improved PO_2 by about 55%. The change in PO_2 significantly but negatively correlated with changes in serum creatinine concentrations which indicated the more increment in PO_2, the more likely serum creatinine concentration to decrease (or alternatively the less likely to rise) postcontrast. The mechanisms by which improved oxygenation protects against creatinine rise and CIN development remain elusive to the most part. This is because our understanding of the pathophysiology of CIN is still in its infancy and little is known regarding the involved processes at the cellular level. However, current evidence suggests that renal hypoxia is an integral element in the pathophysiology of CIN.[13] The processes by which contrast media augments tissue hypoxia are manifold. The sheer volume of contrast media occupies renal vessels thereby impairing effective renal perfusion maintained at normal states.[14] Contrast media viscosity may also lead to increased tubular viscosity which in turn results in decreased urine flow and further retention of contrast agent.[15,16] On the other hand, forced osmotic diuresis and natriuresis induced in particular by hyperosmolar agents leads to afferent arteriole constriction via the tubuloglomerular feedback.[17] Hypoxia is further escalated since following administration of contrast media, renal tissue's oxygen demand substantially increases.[18] Collectively, this supply-demand imbalance culminates in hypoxia and subsequent reactive oxygen species induced cellular damage clinically identified as CIN.[13] Administration of nasal oxygen is believed to mitigate the imbalance by providing an added supply.

Female sex has been suggested to be a risk factor for contrast nephropathy by some studies,[19] and no sex difference in CIN incidence has been reported by others.[20] In our sample of patients undergoing cardiac catheterization however, male sex emerged as a risk factor for CIN; male patients in our study were 3.6 times more likely to develop CIN. This finding is perhaps explained by the fact that compared to females, enrolled male patients in this clinical trial were on average older and also were more likely to have GFR levels below 60 mL/ min/ 1.73 m^2 (data not shown). The correlation of the protocol was significant statistically but not clinically ($r < 0.2$).

This study had some limitations will need to be considered when interpreting the data. It was not designed for subgroup analysis; thus, it caused negative results. Moderate and severe CKD patients also were omitted.

CONCLUSIONS

Based on the present randomized clinical trial, supplementation with nasal oxygen in addition to standard hydration appears to be an effective strategy in reducing CIN. The effect size for this intervention is moderate and the efficacy in certain at-risk patient groups seems to be limited. These findings are to be corroborated by large multicenter trials with longer duration of follow-up to elucidate whether benefits observed in short-term do translate to long-term preservation of kidney function and ultimately reduced mortality risk.

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CONFLICT OF INTEREST

None declared.

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