Preventive Effect of Trimetazidine on Contrast-Induced Acute Kidney Injury in CKD Patients Based on Urinary Neutrophil Gelatinase-associated Lipocalin (uNGAL): A randomized Clinical Trial

Amirhossein Mirhosseini,[1] Behzad Farahani,[2] Alireza Gandomi-Mohammadabadi,[3] Hossein keyvani,[4] Maryam Biglari-Abhari,[1] Alireza Davari,[3] Mohammadhossein Vazirizadeh-Mahabadi,[3] Shokoufeh Savaj[5]

[1]Firoozgar Hospital, Iran University of Medical Science, Tehran, Iran
[2]Department of Cardiology, Firoozgar Hospital, Iran University of Medical Science Tehran, Iran
[3]Student Research Committee, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[4]Department of Virology Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran
[5]Department of Nephrology, Firoozgar Hospital, Iran University of Medical Science, Tehran, Iran

Keywords. trimetazidine, neutrophil gelatinase-associated lipocalin, contrast-induced acute kidney injury

Introduction. Contrast-induced Acute Kidney Injury (CI-AKI) is a prevalent complication of chronic kidney disease (CKD) patients. The aim of this study was to evaluate the effects of periprocedural administration of trimetazidine as an anti-oxidant agent on the incidence of CI-AKI in CKD patients based on changes of Neutrophil Gelatinase-Associated Lipocalin (uNGAL) level, which has recently been introduced as an early predictor of CI-AKI.

Methods. One hundred CKD patients with a mean GFR of 50 ± 7 cc/min who were candidate for coronary angiography assigned randomly to receive (50 patients, intervention group) or not receive (50 patients, control group) trimetazidine (70mg/d) for 72 hours. CI-AKI was defined as 0.5 mg or 25% increase in serum creatinine. We also checked uNGAL before and 12h after angiography.

Results. Serum creatinine, showed a trend of less increment in the case group, although could not achieve a significant difference, there was a significant difference in urinary NGAL rise between two groups. CI-AKI was defined as 1.7 times increase in uNGAL level (12h after angiography to pre-procedurally uNGAL level ratio) according to the ROC curves. The incidence of CI-AKI according to urinary NGAL definition was 8% in the Trimetazidine group and 24% in the control group ($P < .05$).

Conclusion. We concluded that Trimetazidine treatment before angiography may be effective in CI-AKI prevention. Moreover, it is shown that 1.7 times increase in urine NGAL after angiography is a valuable cut off point for clinicians to discriminate high risk patients for contrast nephropathy.

IJKD 2019;13:191-7
www.ijkd.org

Original Paper

INTRODUCTION

Contrast-Induced acute kidney injury (CI-AKI), a sudden deterioration of renal function resulting from contrast media injection, is known as the third most common causes of hospital-acquired acute kidney injury (AKI).[1,2] Among well-known risk factors of CI-AKI like chronic kidney disease (CKD), diabetes mellitus and aging,[3] modality of interventions has an effect on incidence of CI-AKI. Intra-arterial injections, such as coronary angiography with a higher dose of contrast exposure are associated with the highest incidence rate of CI-AKI.[4,5] As seen in most cases, it presents with a non-oliguric acute renal injury and an

asymptomatic transient decline in renal function. CI-AKI was defined as an absolute increase of serum creatinine > 0.5 mg/dl or 25% increase of serum creatinine from baseline in 48-72 hours after exposure when alternative explanations for renal impairment have been excluded.[6,7] Recently urine Neutrophil Gelatinase-associated Lipocalin (uNGAL) has been highlighted as a novel marker for early detection of acute kidney injury.[8] It has small molecular size (25 kDa), excreted and detected in urine and is resistant to degradation. After nephrotoxic and ischemic damage, NGAL is highly accumulated in human kidney cortical tubules, blood and urine.[9] It may become one of the most reliable next-generation biomarkers in the diagnostic, predictive and clinical field of human AKI.[5] Ischemia-reperfusion injury, reactive oxygen radical formation, and direct tubular damage due to injection of contrast media have been introduced as the mechanistic causes of CI-AKI.[10-13] Numerous trials have been conducted to evaluate different pharmacological agents for prevention of CI-AKI. The majority of them were unable to determine any benefit in decreasing CI-AKI incidence rate.[14]

It was previously demonstrated that a cellular anti-ischemic agent Trimetazidine (TMZ) has beneficial impacts during ischemia-reperfusion at the cellular as well as mitochondrial level. Moreover, TMZ has strong antioxidant effects on a variety of tissue preparations.[15,16]

Based on the assumption that there might be involvement of reactive oxygen radicals in the pathogenesis of CI-AKI, we hypothesized that TMZ might be useful in preventing CI-AKI following coronary angiography procedures. From another aspect, some studies have shown uNGAL is more sensitive than serum NGAL in the projection of contrast-induced nephropathy.[17-22] However, this biomarker is not validated quantitatively. We designed this study to find a comparable cutoff point for CI-AKI prediction.

MATERIALS AND METHODS

This study was a single blind, randomized, controlled trial in CKD patients who were candidates for coronary angiography (angioplasty in 82 patients and just angiography in 18 patients). The study was carried out in Firoozgar hospital from March 2016 to September 2017. After approval of the ethical committee of Iran university and registration in *IRCT.ir* (IRCT20171004036555N1), we included those CKD patients with estimated Glomerular Filtration Rate (eGFR) 30-60 cc/min if ejection fraction was more than 45% with no urgent indication for angiography. Patients with contraindication of taking Trimetazidine (e.g. Parkinsonism, severe tremors and severe renal impairment with a creatinine clearance below 30 mL/min, allergy to contrast media, active inflammation and unstable kidney function) were excluded (Figure 1). Contrast nephropathy was defined when absolute serum creatinine increase > 0.5 mg/dL or relative increase > 25% in serum creatinine at 48–72h after exposure to contrast agent compared to baseline serum creatinine values. We also decided to measure uNGAL as a marker of AKI to increase the sensitivity and Mehran score to calculate CI-AKI risk in each group. After evaluation of 681 coronary angiography candidates, 100 patients met our inclusion criteria. Patients enrolled in study were 44 male and 56 female with the mean age of 66.1 ± 6.3 years and mean eGFR = 50.6 ± 7.47 (Range 30-60) mL/min calculated based on CKD-EPI equation (GFR = 141 * min (Scr/κ, 1) α * max (Scr/κ, 1) -1.209 * 0.993 Age * 1.018 [if female] * 1.159 [if black]).[23] They were randomly divided into intervention or control groups. All patients filled a written consent and the local ethics committee approved the protocol. After routine evaluations including history, physical examination, laboratory assessment, and echocardiography, all patients received parenteral hydration in the form of isotonic saline 1 ml/kg body weight per hour starting 12h before angiography up to 12h after. The intervention group also received Trimetazidine 35 mg twice daily orally starting 48h before the procedure up to 24h after the procedure. Visipaque (non-ionic, 320mg I/mL, GE healthcare, Ireland) used in all procedures from femoral access. Prior to coronary angiography, serum creatinine and urea concentrations were measured and repeated 24h, and 48h after the procedure. Urine samples also were gathered before and 12h after angiography, centrifuged and stored at -80°C and ultimately measured by NGAL ELISA Kit (Human, Bioportoshop, 10-1000 ng/mL, Denmark).

Statistical Analysis

SPSS software version 22.0.0 (IBM Corp., Armonk, NY, USA) was used to analyze the provided data.

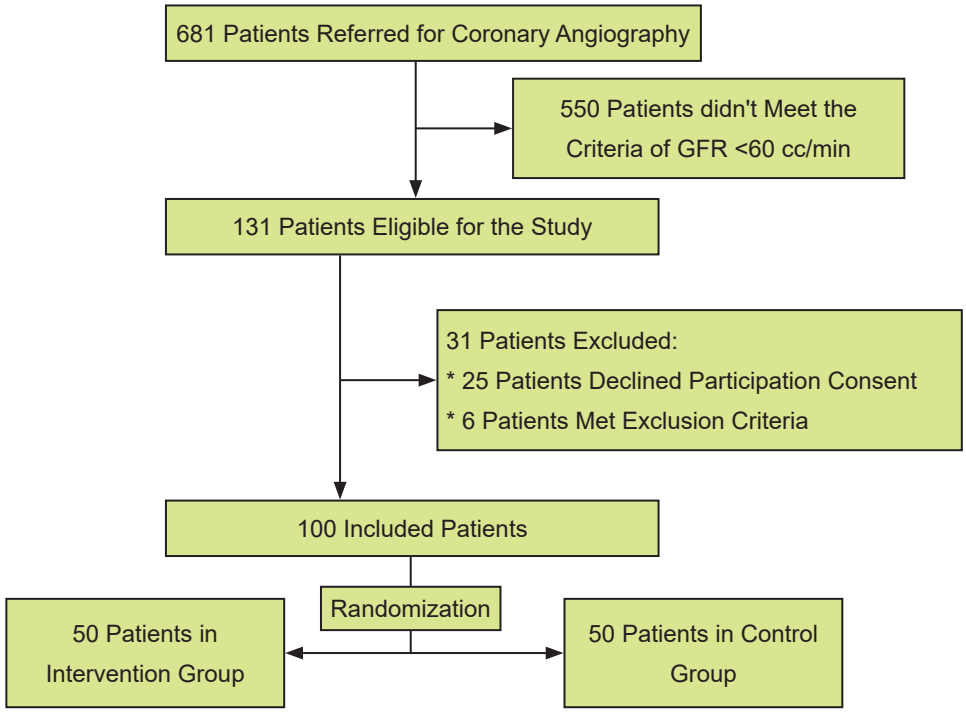

Figure 1. Diagram showing the Enrollment and Randomization

Continuous variables with normal distribution were described using means ± standard deviation and those with a non-normal distribution as median and interquartile range. Comparison between groups was conducted through independent *t* test and assessment of the differences between re-measured variables was done by repeated measurement analysis. To check the association between binary or ordinal qualitative variable, we used chi-square test. Correlations between uNGAL and other variables were evaluated by Pearson's or Spearman's rank correlation coefficient test. To estimate the sensitivity and specificity of uNGAL level for the diagnosis of CI-AKI, receiver-operating characteristic (ROC) curves were generated and the area under the curve (AUC) was calculated. We defined the cut-off as closest point to sensitivity and (1-specificity) = 1.0 on ROC curve. In all tests, differences were considered significant at 5%.

RESULTS

Among 681 patients that were introduced for elective coronary angiography, 550 patients were excluded because of the GFR > 60 mL/min in the first step. Thirty-one patients did not accept participation consent or met one or more of exclusion criteria, therefore were excluded (Figure 1). Finally, the overall analysis consisted of 100 patients (50 in the control group 50 in the intervention group) with a mean age of 66.1 ± 6.3 years. The mean baseline serum creatinine was 1.28 ± 0.18 mg/dL. The mean baseline uNGAL was 97.9 ± 79.7 ng/mL. Laboratory results and patient's data was extracted from the patient's chart. Demographic characteristic data between two groups i.e. the intervention and control group are presented in Table 1.

Two group of Patients had no significant difference in demographic characteristics and risk factors including age, gender, eGFR, contrast dose, ejection fraction, history of diabetes mellitus, and hypertension ($P > .05$). CI-AKI occurred in 14 patients (14%) based on its definition with serum creatinine level. In the intervention group, 4 (8%) of 50 patients developed CI-AKI compared to 10 (20%) of 50 patients in the control group ($P > .05$). Data analysis also showed a significant rise in serum creatinine before and after the procedure in the control group ($P < .05$). However, there was no significant change in serum creatinine in the intervention group ($P > .05$) (Figure 2). The intervention group had a lower incidence of CI-AKI compared with the control group; nevertheless, it did not show a significant difference ($P > .05$).

Table 1. Demographic and Clinical Characteristics Between Two Groups Intervention and Control Group (n = 100)

Characteristic	Intervention Group	Control Group	*P*
Number of Subject	50	50	
Age, y	65 ± 6	67 ± 6	> 0.05
Men / Women	20/30	24/26	> 0.05
Weight, kg	66 ± 6	66 ± 5	> 0.05
Ejection Fraction (%)	51 ± 4	51 ± 5	> 0.05
Baseline Urinary NGAL, ng/mL	95 ± 70	101 ± 89	> 0.05
eGFR, cc/min	50 ± 7	50 ± 8	> 0.05
Hemoglobin, g/dL	13.4 ± 1	12.76 ± 2	> 0.05
Baseline Serum Creatinine, mg/dL	1.27 ± 0.15	1.29 ± 0.15	> 0.05
Hypertension (%)	68	56	> 0.05
Diabetes Mellitus (%)	64	62	> 0.05
Contrast Dosage, mL/min	116.80	121.80	> 0.05
Mehran Score	8 ± 2	8 ± 2	> 0.05

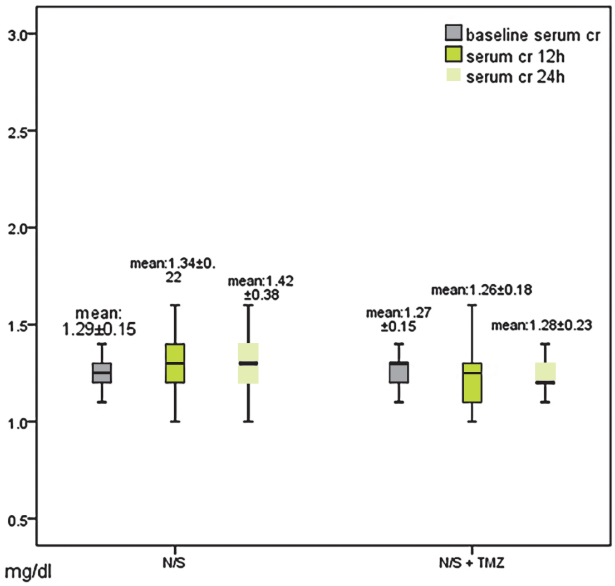

Figure 2. Comparison Between 2 Groups Regarding Serum Creatinine Peri- procedurally

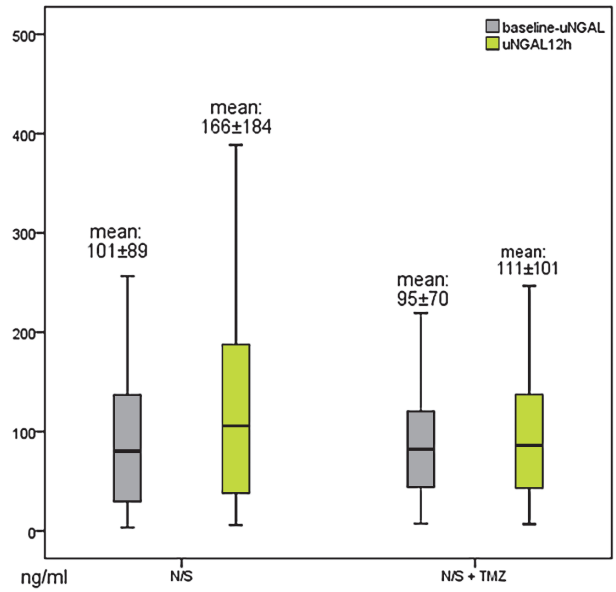

Figure 3. Comparison Between 2 Groups Regarding uNGAL Peri-procedurally

uNGAL inversely correlated with eGFR ($P < .05$) and its increment level among intervention and control groups were (16.04 ± 48.55 vs. 87.77 ± 188.30 ng/mL), respectively ($P < .05$) (Figure 3). Based on CI-AKI definition, the best AUC of uNGAL for diagnosis CI-AKI with a sensitivity of 87% and specificity of 92% were 0.96 ± 0.018 ($P < .05$) (Figure 4). According to the ROC curve, a 1.7 times rise in uNGAL level (12 hours after angiography to pre-procedurally uNGAL level ratio (uNGAL12 / uNGAL0) had positive and negative predictive values of 63.2% and 97.5%, respectively. Regarding the uNGAL cutoff point of 1.7 times, the overall incidence of CI-AKI was 16%. There were 4 patients (8%) in the intervention group in comparison with 12 patients (24%) in the control group ($P < .05$), which confirmed the protective effect of TMZ in the intervention group (Table 2). No potential side effects relevant to TMZ administration were reported during the study.

DISCUSSION

Acute kidney injury (AKI) is associated with increased morbidity, mortality, cost and decreased quality of life especially in patients with comorbid diseases.[24] There is a global health system decision to lower the rate of AKI till 2025. At this point, all preventable causes of AKI should be eliminated.CI-AKI is a prevalent cause of AKI that its incidence rate can approximate to 50% in high-risk patients.

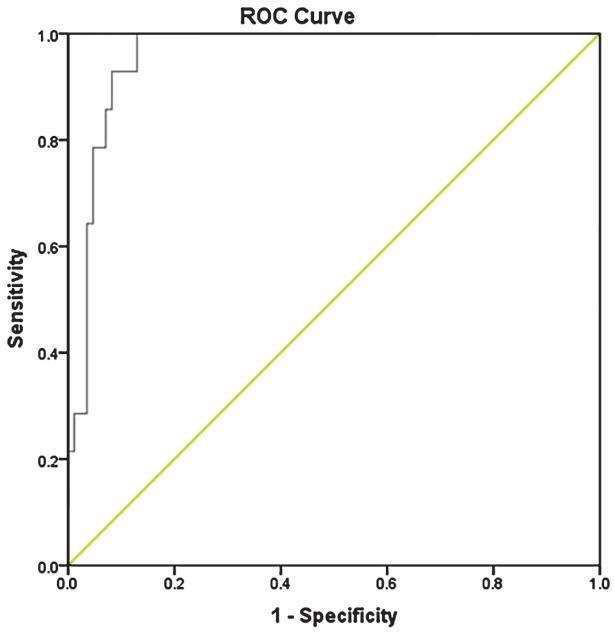

Figure 4. Predictive Performance of uNGAL 12/uNGAL 0 in Diagnosis of AKI

Table 2. Comparison of CI-AKI Incidence Rate According to Serum Creatinine and uNGAL Definition

Variables	Intervention Group N = 50	Control Group N = 50
CI-AKI Incidence According to Serum Cr Definition	4 (8%)	10 (20%)
CI-AKI Incidence According to Urinary NGAL Definition	4 (8%)	12 (24%)

Different approaches to decrease CI-AKI have been introduced and most of them were not validated in large studies and meta-analysis. It seems that these failures can have two justifications: inappropriate method for prevention or misdiagnosis of CI-AKI due to creatinine based diagnosis. We decided to overcome these two problems in our study. First, we had the knowledge that the pathophysiology of contrast nephropathy is direct toxicity and ischemia. It decreases the antioxidant enzyme activity in the nephron and consequently direct cytotoxicity to the renal cells.[25,26] TMZ has been introduced as an effective drug to improve exercise tolerance and cardiac function in patients with ischemic heart disease.[27] Noble et al. has shown in myocardial ischemia model in rabbits, that TMZ can decrease the infarct size.[28] Experimental studies have reported that during cellular ischemia TMZ retains the intracellular concentration of ATP and inhibits the extracellular leakage of potassium. In this study, we used the effective dose in ischemic heart disease (35 mg Trimetazidine, twice daily, for 72h starting from 48h before the procedure). Second was the method of diagnosis, as we know all of the studies and guideline criteria for the diagnosis of AKI is creatinine based. Since creatinine level has not enough sensitivity, it could not diagnose subclinical cases. On the other hand, it needs at least 24-72 hours for detection of CI-AKI. NGAL has been introduced as a biomarker to diagnose CI-AKI in earlier stages.[29] It is a reliable diagnostic biomarker for AKI since its serum and urinary levels rise after two hours when patients exposed to contrast and exhibits better sensitivity than serum creatinine alone.[30] In a meta-analysis which included 19 studies and more than 2500 patients, Hasse et al. showed urinary NGAL has a more sensitivity in comparison with plasma NGAL in diagnosis of acute kidney Injury and a urinary cut-off NGAL > 150 ng/mL on a standardized platform was suggested to have optimal sensitivity and specificity to predict acute kidney injury.[31] Since there is a large variability in urine NGAL especially higher levels in patients with chronic kidney disease,[32] we decided to use urinary NGAl ratio before and after the procedure. We validated our NGAl results based on the creatinine-based definition of CI-AKI. As presented, there was a 14% incidence rate of contrast nephropathy, but 2 out of 100 patients had a significant increase in urinary NGAL with no creatinine change. We found a 1.7 ratio of uNGAL before, 12 hours after procedure have a sensitivity (87%), and specificity (92%) based on the ROC curve. Our study revealed that TMZ with normal saline injection in CKD patients can significantly decrease the risk of CI-AKI incidence ($P < .05$) as respects on CI-AKI definition based on uNGAL (uNGAL12 / uNGAL0) (Table 2).

Akgüllu in 2014 reported the prophylactic effect of TMZ in 24 Wistar rat[33] that his study approved in the human setting by Shehata who published his study on 100 patients with diabetes mellitus and showed a preventive effect of TMZ on CI-AKI.[34] On 2017, Ibrahim et al evaluated the preventive effect of TMZ in one hundred chronic kidney disease patients with eGFR < 90 cc/min. They reported a significant difference regarding the rate of CI-AKI among TMZ versus control groups (10% vs. 26%).[35] A meta-analysis by Natkarni and coworkers in 290 patients was also in support of TMZ preventive

effect in CI-AKI.[36] We confirmed the TMZ effect by a more sensitive marker of AKI.

Several limitations during the project should take in to consideration. Our study had a relatively small sample size and was single blind. The dosage of oral TMZ was derived from the standard therapeutic regimen of myocardial ischemia, it is possible that a loading dose of TMZ has a more preventive role in CI-AKI. We excluded patients with CKD 4 and 5 due to drug recommendations. Accordingly, the results of this study could not extend to these patients' population.

CONCLUSION

TMZ administration had a protective effect on prevention of CI-AKI in our study. Our results should be reevaluated in a larger study with different doses of TMZ. We also concluded that a cutoff point of 1.7 times rise in uNGAL, 12 hours after angiography to pre-procedurally uNGAL level ratio can discriminate high risk patients for CI-AKI. This cutoff point can guide us to early diagnosis, decreasing hospitalization in low-risk cases, and better patient support.

REFERENCES

1. Katzberg RW, Lamba R. Contrast-induced nephropathy after intravenous administration: fact or fiction? Radiol Clin North Am. 2009; 47(5):789-800.
2. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. Am J Kidney Dis. 2002; 39(5):930-6.
3. Katzberg RW, Newhouse JH. Intravenous contrast medium-induced nephrotoxicity: is the medical risk really as great as we have come to believe? Radiology. 2010; 256(1):21-8.
4. Mehran R, Nikolsky E. Contrast-induced nephropathy: definition, epidemiology, and patients at risk. Kidney Int Suppl. 2006(100):S11-5.
5. Bolignano D, Donato V, Coppolino G, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a marker of kidney damage. Am J Kidney Dis. 2008; 52(3):595-605.
6. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999; 130(6):461-70.
7. Andreucci M, Solomon R, Tasanarong A. Side effects of radiographic contrast media: pathogenesis, risk factors, and prevention. Biomed Res Int. 2014; 2014:741018.
8. Mishra J, Dent C, Tarabishi R, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet. 2005; 365(9466):1231-8.
9. Mori K, Lee HT, Rapoport D, et al. Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury. J Clin Invest. 2005; 115(3):610-21.
10. Baliga R, Ueda N, Walker PD, Shah SV. Oxidant mechanisms in toxic acute renal failure. Am J Kidney Dis. 1997; 29(3):465-77.
11. Gami AS, Garovic VD. Contrast nephropathy after coronary angiography. Mayo Clin Proc. 2004; 79(2):211-9.
12. Bakris GL, Lass N, Gaber AO, Jones JD, Burnett JC, Jr. Radiocontrast medium-induced declines in renal function: a role for oxygen free radicals. Am J Physiol. 1990; 258(1 Pt 2):F115-20.
13. Yoshioka T, Fogo A, Beckman JK. Reduced activity of antioxidant enzymes underlies contrast media-induced renal injury in volume depletion. Kidney Int. 1992; 41(4):1008-15.
14. Aydogdu S. [Contrast-induced nephropathy]. Turk Kardiyol Dern Ars. 2013; 41(1):28-30.
15. Elimadi A, Settaf A, Morin D, et al. Trimetazidine counteracts the hepatic injury associated with ischemia-reperfusion by preserving mitochondrial function. J Pharmacol Exp Ther. 1998; 286(1):23-8.
16. Aubert A, Bernard C, Clauser P, Harpey C, Vaudry H. Effect of phenazine methosulfate on electrophysiological activity of the semicircular canal: antioxidant properties of trimetazidine. Eur J Pharmacol. 1989; 174(2-3):215-25.
17. Mori K, Nakao K. Neutrophil gelatinase-associated lipocalin as the real-time indicator of active kidney damage. Kidney Int. 2007; 71(10):967-70.
18. Schmidt-Ott KM, Mori K, Li JY, et al. Dual action of neutrophil gelatinase-associated lipocalin. J Am Soc Nephrol. 2007; 18(2):407-13.
19. Devarajan P. Emerging biomarkers of acute kidney injury. Contrib Nephrol. 2007; 156:203-12.
20. Coca SG, Yalavarthy R, Concato J, Parikh CR. Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. Kidney Int. 2008; 73(9):1008-16.
21. Waikar SS, Bonventre JV. Biomarkers for the diagnosis of acute kidney injury. Curr Opin Nephrol Hypertens. 2007; 16(6):557-64.
22. Nickolas TL, O'Rourke MJ, Yang J, et al. Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. Ann Intern Med. 2008; 148(11):810-9.
23. Levey AS, Inker LA, Coresh J. GFR estimation: from physiology to public health. Am J Kidney Dis. 2014; 63(5):820-34.
24. Johansen KL, Smith MW, Unruh ML, et al. Predictors of health utility among 60-day survivors of acute kidney injury in the Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network Study. Clin J Am Soc Nephrol. 2010; 5(8):1366-72.
25. Hizoh I, Haller C. Radiocontrast-induced renal tubular cell apoptosis: hypertonic versus oxidative stress. Invest Radiol. 2002; 37(8):428-34.
26. Hizoh I, Strater J, Schick CS, Kubler W, Haller C. Radiocontrast-induced DNA fragmentation of renal tubular

cells in vitro: role of hypertonicity. Nephrol Dial Transplant. 1998; 13(4):911-8.

27. Brottier L, Barat JL, Combe C, Boussens B, Bonnet J, Bricaud H. Therapeutic value of a cardioprotective agent in patients with severe ischaemic cardiomyopathy. Eur Heart J. 1990; 11(3):207-12.
28. Noble MI, Belcher PR, Drake-Holland AJ. Limitation of infarct size by trimetazidine in the rabbit. Am J Cardiol. 1995; 76(6):41B-4B.
29. Goldstein SL. Acute kidney injury biomarkers: renal angina and the need for a renal troponin I. BMC Med. 2011; 9:135.
30. Clerico A, Galli C, Fortunato A, Ronco C. Neutrophil gelatinase-associated lipocalin (NGAL) as biomarker of acute kidney injury: a review of the laboratory characteristics and clinical evidences. Clin Chem Lab Med. 2012; 50(9):1505-17.
31. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A, Group NM-aI. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis. 2009; 54(6):1012-24.
32. Woo KS, Choi JL, Kim BR, Kim JE, An WS, Han JY. Urinary neutrophil gelatinase-associated lipocalin levels in comparison with glomerular filtration rate for evaluation of renal function in patients with diabetic chronic kidney disease. Diabetes Metab J. 2012; 36(4):307-13.
33. Akgullu C, Saruhan T, Eryilmaz U, et al. The first histopathological evidence of trimetazidine for the prevention of contrast-induced nephropathy. Ren Fail. 2014; 36(4):575-80.
34. Shehata M. Impact of trimetazidine on incidence of myocardial injury and contrast-induced nephropathy in diabetic patients with renal dysfunction undergoing elective percutaneous coronary intervention. Am J Cardiol. 2014; 114(3):389-94.
35. Ibrahim TA, El-Mawardy RH, El-Serafy AS, El-Fekky EM. Trimetazidine in the prevention of contrast-induced nephropathy in chronic kidney disease. Cardiovasc Revasc Med. 2017; 18(5):315-9.
36. Nadkarni GN, Konstantinidis I, Patel A, et al. Trimetazidine Decreases Risk of Contrast-Induced Nephropathy in Patients With Chronic Kidney Disease: A Meta-Analysis of Randomized Controlled Trials. J Cardiovasc Pharmacol Ther. 2015; 20(6):539-46.

Correspondence to:
Shokoufeh Savaj, MD
Department of Nephrology, Firoozgar Hospital, Iran University of Medical Science, Tehran, Iran
E-mail: ssavaj@hotmail.com

Received August 2018
Revised October 2018
Accepted December 2018