ANSWERS TO REVIEWERS

March 16, 2017

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name:).

Title: CONTRAST-INDUCED ACUTE KIDNEY INJURY: A REVIEW OF PRACTICAL POINTS

Authors: Sercin Ozkok, Abdullah Ozkok

Name of Journal: *World Journal of Nephrology*

ESPS Manuscript NO: 02715846

The manuscript has been improved according to the suggestions of reviewers.

Thank you for your consideration of our manuscript for publishing in the *World Journal of Nephrolgy.*

Sincerely yours,

Abdullah OZKOK, MD, Assoc. Prof.

Address: Saglik Bilimleri University, Umraniye Training and Research Hospital, Department of Nephrology, Umraniye, Istanbul, Turkey

Email: abdullahozkok@yahoo.com

Phone: +902166321818

Fax: +902166327124

REVIEWER 1 (Reviewer no: *01593993)*:

The authors reviewed the state-of-the-art of contrast induced acute kidney disease. Most issues have been tackled and summarized. Tables help summarize the evidence. Paper is well written. In my view, there is an important risk score that has not been mentioned and is frequently used by interventional cardiologists, the Mehran score (J Am Coll Cardiol. 2004 Oct 6;44(7):1393-9.). This score has prognostic implications and should be added in this review.

We thank the reviewer for this valuable contribution. We have added a new section entitled: "Risk scoring for CI-AKI" and discussed Mehran and ACEF risk scoring systems.

RISK SCORING FOR CI-AKI:

Several risk scoring systems have been developed to predict the CI-AKI. In the study by Mehran et al (1), CI-AKI was defined as an increase ≥ 25% and/or ≥0.5 mg/dL in serum creatinine at 48 h after PCI and they proposed a CI-AKI risk stratification score based on 8 readily available variables including 1) patient-related features such as age>75 years, diabetes mellitus, chronic congestive heart failure (CHF), acute pulmonary edema, hypotension, anemia, and chronic kidney disease; 2) procedure-related features such as the use of IABP or increasing volumes of CM. Integer scores of these risk factors were determined as: hypotension, 5; IABP, 5; CHF,5; age>75 years, 4; anemia, 3; diabetes mellitus,3; each 100 mL of CM, 1; serum creatinine >1.5 mg/dL, 4; eGFR=40-60 mL/min/1.73 m^2:2; eGFR=20-40 mL/min/1.73 m^2, 4; eGFR<20 mL/min/1.73 m^2, 6. These scores are summed up and total risk score is obtained. For example, if total risk score is ≤ 5, risk of CI-AKI is 7.5% and risk of dialysis is 0.04%. However risk of CI-AKI is 57% and risk of dialysis is approximately 13% with a total risk score of ≥ 16. In conclusion, in this study, increasing total risk score was found to exponentially predict increased CI-AKI risk. Another simple risk scoring for CI-AKI in patients undergoing PTCI is composed of age, creatinine and ejection fraction (ACEF score) which has been found to be an independent and useful predictor of CI-AKI defined as a rise in serum creatinine ≥0.5 mg/dL (2,3).

1- Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses

JW, Stone GW, Leon MB, Dangas G. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol. 2004; 6;44(7):1393-9. [PMID: 15464318 DOI: 10.1016/j.jacc.2004.06.068]

2- Ranucci M, Castelvecchio S, Menicanti L, Frigiola A, Pelissero G. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. Circulation. 2009; 119: 3053–3061 [PMID: 19506110 DOI: 10.1161/CIRCULATIONAHA.108.842393]

3- Capodanno D, Ministeri M, Dipasqua F, Dalessandro V, Cumbo S, Gargiulo G, Tamburino C. Risk prediction of contrast-induced nephropathy by ACEF score in patients undergoing coronary catheterization. J Cardiovasc Med (Hagerstown). 2016;17(7):524-9 [PMID: 25304032 DOI: 10.2459/JCM.0000000000000215]

Minor issues: Please correct "Conrast (PC)" in table 9.

We apologize for this mistake. Misspelling was corrected.

Please write the references in an homogeneus manner (sometimes year appears at the end, sometimes after the title...)

References were re-arranged according to journal style.

REVIEWER 2 (Reviewer no: *00068723*):

This manuscript reviewed acute kidney injury (AKI) due to contrast-media. The message of this manuscript is practical and important to all the employees in clinics and hospitals. The manuscript was written from practical point of view, and useful. Mechanism of AKI due to contrast-media would pave a way to prevent AKI due to contrast medium. It would be appropriated to expand the mechanism of AKI related with contrast-medium. Many of the readers know AKI due to contrast-medium. But not many of them are encountered with the condition. It would be helpful to expand the symptoms, treatment, and prognosis of AKI due to contrast-medium.

We thank the reviewer for the favorable comments and suggestions. As requested, we expanded the various parts of the manuscript including pathophysiological mechanisms, treatment and preventive

strategies.

PATHOPHYSIOLOGY OF CI-AKI:

In normal physiological state, renal medullary blood flow and oxygen tension are relatively lower than those of the renal cortex. Furthermore, thick ascending limb located in the outer part of the renal medulla has a high-rate of ion transport with increased oxygen consumption exacerbating the relative hypoxia of the renal medulla. The most susceptible part of the nephron to hypoxia is well-known to be the renal medulla. CM is shown to decrase the oxygen tension of the renal medulla and simultaneously CM-induced osmotic diuresis causes increased sodium delivery to thick ascending limb leading to increased oxygen demand (1,2). CM is known to cause direct mesangial and tubular cell toxicity. Proposed mechanisms of CM-induced cytotoxicity include oxidative stress, cellular energy failure, impaired cellular calcium homeostasis and increased apoptosis (3-6). In the study by Peer et al, iodinated CM at different concentrations was found to induce apoptosis in both mesangial and tubular cells (7). The relationship between hypoxia, oxidative stress and direct cytotoxicity is not well-understood in the context of CI-AKI. Previously, a mismatch between the metabolic demands and the perfusion of renal medulla, in another words "relative hypoxia" was suggested to cause increased oxidative stress leading to further cytotoxicity (8). However, recently, in the study by Liu et al, CM-induced direct cytotoxicity has been shown to cause increased oxidative stress even in the absence of hypoxia. Oxidative stress seemed to be a consequence not a cause of renal tubular injury. Furthermore, in this study CA was found to increase tubuloglomerular feedback which might contribute to disturbances of renal perfusion and filtration (9). It may suggested that direct cytotoxicity of CA may be the primary event that pull the trigger rather than hypoxia, hypoperfusion or oxidative stress in the pathopysiological mechanism of CI-AKI.

1- Cronin RE. Contrast-induced nephropathy: pathogenesis and prevention. Pediatr Nephrol. 2010;25(2):191-204 [PMID: 19444480 DOI: 10.1007/s00467-009-1204-z]

2-Heyman SN, Brezis M, Epstein FH, Spokes K, Silva P, Rosen S . Early renal medullary hypoxic injury from radiocontrast and indomethacin. Kidney Int. 1991; 40:632–642 [PMID: 1745012]

3- Itoh Y, Yano T, Sendo T, Sueyasu M, Hirano K, Kanaide H, Oishi R. Involvement of de novo ceramide synthesis in radiocontrast-induced renal tubular cell injury. Kidney Int 2006;69:288–297

[PMID: 16408118 DOI: 10.1038/sj.ki.5000057]

4- Schick CS, Haller C. Comparative cytotoxicity of ionic and non-ionic radiocontrast agents on MDCK cell monolayers in vitro. Nephrol Dial Transplant 1999; 14:342–347 [PMID: 10069186]

5- Peer A, Averbukh Z, Berman S, Modai D, Averbukh M, Weissgarten J. Contrast media augmented apoptosis of cultured renal mesangial, tubular, epithelial, endothelial, and hepatic cells. Invest Radiol 2003;38:177–182 [PMID: 12595799 DOI: 10.1097/01.RLI.0000054529.61167.84]

6- Haller C, Hizoh I. The cytotoxicity of iodinated radiocontrast agents on renal cells in vitro. Invest Radiol 2004; 39:149–154 [PMID: 15076007]

7-Peer A, Averbukh Z, Berman S, Modai D, Averbukh M, Weissgarten J. Contrast media augmented apoptosis of cultured renal mesangial, tubular, epithelial, endothelial, and hepatic cells. Invest Radiol 2003;38:177–182 [PMID: 12595799 DOI: 10.1097/01.RLI.0000054529.61167.84]

8- Heyman SN, Rosen S, Khamaisi M, Idée JM, Rosenberger C. Reactive oxygen species and the pathogenesis of radiocontrast-induced nephropathy. Invest Radiol 2010; 45:188–195. [PMID: 20195159 DOI: 10.1097/RLI.0b013e3181d2eed8]

9- Liu ZZ, Schmerbach K, Lu Y, Perlewitz A, Nikitina T, Cantow K, Seeliger E, Persson PB, Patzak A, Liu R, Sendeski MM. Iodinated contrast media cause direct tubular cell damage, leading to oxidative stress, low nitric oxide, and impairment of tubuloglomerular feedback. Am J Physiol Renal Physiol 2014; 306:F864–F872. [PMID: 24431205 DOI: 10.1152/ajprenal.00302.2013]

TREATMENT OF CI-AKI:

There is no specific treatment for CI-AKI. There is no evidence that any of the preventive strategies are helpful once the CI-AKI develops. Similar to the management of other types of AKI, stabilization of hemodynamic paramaters and maintenance of normal fluid and electrolyte balance is crucial. Thus, prevention may be the only treatment modality for CI-AKI.

Intravenous hydration:

In a prospective randomized study, hydration with isotonic (0.9% saline) and half-isotonic (0.45% sodium chloride plus 5% glucose) solutions were compared in terms of efficiency in prevention of CI-AKI in patients undergoing coronary angioplasty. Hydration was performed

before, during and after the procedure and total amount of hydration was approximately 2000 mL. In this study, isotonic hydration was found to be superior to half-isotonic hydration in the prevention of CI-AKI (1). In a study performed on patients undergoing nonemergency cardiac catheterization, saline hydration starting from 12 h before the procedure was compared to unrestricted oral fluid intake (2). Patients in the first group received normal saline for 24 h (at a rate of 1 mL/kg/h). Intravenous saline hydration was found to decrease the both incidence and severity of CI-AKI. In contrast, in a very recent prospective, randomized, non-inferiority study perfomed on CKD patients (eGFR: 30-59 mL/min/1.73 m^2) undergoing an elective procedure with CM, patients were randomly assigned to receive intravenous 0.9% NaCl or no prophylaxis (3). No prophylaxis group was found to be non-inferior to prophylaxis group and furthermore it was found to be cost-effective. However, despite the results of this study, we still strongly recommend hydration especially in patients with high risk of CI-AKI. Hypervolemia should be avoided during hydration of the patients. Further studies are needed to prove the efficacy of hydration in prevention of CI-AKI.

1- Mueller C, Buerkle G, Buettner HJ, Petersen J, Perruchoud AP, Eriksson U, Marsch S, Roskamm H. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. Arch Intern Med 2002;162(3): 329–336 [PMID: 11822926]

2- Trivedi HS, Moore H, Nasr S, Aggarwal K, Agrawal A, Goel P, Hewett J.. A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity. Nephron Clin Pract 2003; 93:C29–C34.[PMID: 12411756]

3- Nijssen EC, Rennenberg RJ, Nelemans PJ, Essers BA, Janssen MM, Vermeeren MA, Ommen VV, Wildberger JE. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. Lancet. 2017; 20. pii: S0140-6736(17)30057-0 [PMID: 28233565 DOI: 10.1016/S0140-6736(17)30057-0]

Sodium bicarbonate:

There is no standard dose of sodium bicarbonate for the prevention of CI-AKI. In a study, bicarbonate solution was prepared by adding 154 mL of 1000 mEq/L sodium bicarbonate to 846 mL of 5% dextrose in H_2O (1). In this study, hydration with sodium bicarbonate before contrast exposure is more effective than hydration with sodium chloride for prophylaxis of CI-AKI. In another study, bicarbonate solution was prepared with 75 mL of 8.4% sodium bicarbonate added to 1 L of isotonic saline (2). In this study, no difference was found between sodium bicarbonate plus saline group and hyration with only saline group in terms of prevention from CI-AKI. Since sodium bicarbonate contains high amount of sodium, risk of hypervolemia should be taken into consideration especially in patients with congestive heart failure and CKD and dose of the bicarbonate should be individualized.

1- Merten GJ, Burgess WP, Gray LV, Holleman JH, Roush TS, Kowalchuk GJ, Bersin RM, Van Moore A, Simonton CA 3rd, Rittase RA, Norton HJ, Kennedy TP. Prevention of contrastinduced nephropathy with sodium bicarbonate: a randomized controlled trial. JAMA 2004; 291:2328. [PMID: 15150204 DOI: 10.1001/jama.291.19.2328]

2- Vasheghani-Farahani A, Sadigh G, Kassaian SE, Khatami SM, Fotouhi A, Razavi SA, Mansournia MA, Yamini-Sharif A, Amirzadegan A, Salarifar M, Sadeghian S, Davoodi G, Borumand MA, Esfehani FA, Darabian S. Sodium bicarbonate plus isotonic saline versus saline for prevention of contrast induced nephropathy in patients undergoing coronary angiography: a randomized controlled trial. Am J Kidney Dis 2009; 54:610-618. [PMID: 19619921 DOI: 10.1053/j.ajkd.2009.05.016]

N-acetyl cysteine:

There is no consensus on the dose of the NAC however it is usually used at a dose of 600-1200 mg orally twice daily.

REVIEWER 3 (Reviewer no: *00233953*):

Interesting review Comment #1: in addition to NSF, recent literature has raised concern about gadolinium deposition in the brain even in patients with normal kidney function. This is investigated by the European agencies and the FDA Please include.

We thank the reviewer for this comment. As suggested, we included the risk of deposition of gadolinium in the brain.

Recently, a relationship between previous gadolinium administrations and high signal intensity in the several parts of the brain has been suggested independent of renal function (1,2). Gadolinium concentration in tissue was found to be strongly associated with cumulative gadolinium dose (3). Currently, clinical significance of gadolinium deposition in tissues is unclear, further studies are needed to clarify this issue.

1-Kanda T, Ishii K, Kawaguchi H, Kitajima K, Takenaka D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. Radiology 2014;270:834–841 [PMID: 24475844 DOI: 10.1148/radiol.13131669]

2-Olchowy C, Cebulski K, Łasecki M, Chaber R, Olchowy A, Kałwak K, Zaleska-Dorobisz U. The presence of the gadolinium-based contrast agent depositions in the brain and symptoms of gadolinium neurotoxicity - A systematic review. PLoS One. 2017; 10;12(2):e0171704 [PMID: 28187173 DOI: 10.1371/journal.pone.0171704]

3-McDonald RJ, McDonald JS, Kallmes DF, Jentoft ME, Murray DL, Thielen KR, Williamson EE, Eckel LJ. Intracranial Gadolinium Deposition after Contrast-enhanced MR Imaging. Radiology 2015;275:772–782 [PMID: 25742194 DOI: 10.1148/radiol.15150025]