

Maurizio Salvadori, MD, Professor
Editor in Chief,
World Journal of Transplantation
October 12th, 2016

Jin-Xin Kong and Xue-Mei Gong,
Science Editors, Editorial Office

Re: ESPS Manuscript 29707 entitled "Contrast-Induced Acute Kidney Injury in Kidney Transplant Recipients: A Systematic Review and Meta-analysis"

Dear Editor,

Thank you for the thoughtful input and review of our manuscript. The reviewers' inputs are extremely helpful. We believe as a result of this review, our study would have more value for your readers. We revised the manuscript based on the reviewer's suggestions. We have attached our point by point response.

Thank you for your time and consideration. We look forward to hearing from you.

Sincerely,

Wisit Cheungpasitporn, M.D.

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Response to Science Editor, Editorial Office

Comment 1:

Please revise your article according to the reviewers' comments/suggestions and provide point to point responses to each in the letter format specified in the attached files. Please highlight the change according to the comments. Tips in this file do not need to be answered, just revise according to them. Thanks!

Response: We thank you for reviewing our manuscript. We really appreciated your and reviewers' input. We have revised our manuscript as your and reviewers' suggestions.

Response to Reviewer#1

Reviewer's code: 00054120

Reviewer's country: United States

Science editor: Jin-Xin Kong

Date sent for review: 2016-08-26 15:51

Date reviewed: 2016-09-01 07:28

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

Response: We thank you for reviewing our manuscript. We really appreciated your input and found your suggestions very helpful. We revised the manuscript based on your suggestions.

COMMENTS TO AUTHORS

An excellent review article which very well written, I have few questions to the authors
1- what is the incidence of AKI in post-renal transplant recipients at their center. 2- Do you follow certain protocol or guidelines when performing radiological procedures in these patients, such using certain type of IV dye, use of prophylactic NAC and/or well

hydration? 3- Do they think that the incidence of AKI is lower/same or higher at their center and what is the reason for that?

Response: Thank you for raising an important point. This is very excellent question.

1. We are currently conducting a study evaluating the incidence of CIAKI in our institution. The study has not completed yet. Our preliminary data shows the incidence of CIAKI in kidney transplant approximately at 8% and comparable to finding from our current meta-analysis.
2. Briefly, protocols for CIAKI prevention in our institution include
 - 1) Hold offending medication (Diuretics (whenever possible), Metformin, Nonsteroidal anti-inflammatory drugs or cyclooxygenase-2 inhibitors (except for low-dose aspirin)). We do not hold calcineurin inhibitor.
 - 2) Preprocedure hydration as directed in KDIGO guideline.
 - 3) N-acetylcysteine is optional and given case by case per nephrology. Typical dosing starts 12 hours before contrast administration and continues for 48 to 72 hours as follows: Adults: 1,200 mg orally twice daily.
 - 4) We use low-osmolar contrast in our institution.
3. Our preliminary data shows the incidence of CIAKI in kidney transplant approximately at 8% and comparable to finding from our current meta-analysis. The study has not yet completed. Since the data on CIAKI in kidney transplant patients are currently lacking. Thus, we are hoping that our findings from this current meta-analysis may impact the risk stratification for administration of contrast media and CIAKI prevention in kidney transplant recipients.

Response to Reviewer#2

Reviewer's code: 00505314

Reviewer's country: United States

Science editor: Jin-Xin Kong

Date sent for review: 2016-08-26 15:51

Date reviewed: 2016-09-16 01:45

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

Response: We thank you for reviewing our manuscript. We really appreciated your input and found your suggestions very helpful. We revised the manuscript based on your suggestions.

COMMENTS TO AUTHORS

This is meta-analysis of published studies evaluating nephrotoxic risk of contrast agents in kidney transplant recipients. Article is written nicely and methodology looks good. Limitations are the heterogeneous nature of the individual studies. Over all, it appears to be a low risk population since only 3 studies had patients with serum creatinine >1.5 mg/dl. Authors tried to do a sensitivity analysis to account for the osmotically different contrast agents used. It is interesting and reassuring to see that CNI agent use did not affect the risk of contrast induced nephrotoxicity. More studies involving high risk patients are needed to make more definitive conclusions. It will be nice to include a paragraph based on the analysis suggesting the precautions that need to be taken before exposing kidney transplant recipients to radio-contrast agents.

Response: We thank you for reviewing our manuscript. The reviewer raised very important point. We agreed with the reviewer that most included studies assessed CIAKI incidence in a relatively low risk kidney transplant population for CIAKI and this is an important limitation of this study. Thus, we added the point that more studies

involving high risk patients are needed to make more definitive conclusions in our limitations of this study as reviewer's suggestion. The following text in **bold** has been added in limitation section of our manuscript:

"There are several limitations to our study. First, there were statistical heterogeneities in the analysis of the incidence of CIAKI. The potential sources of this heterogeneity included differences in baseline characteristics, types of procedure, and contrast media. Thus, we performed a sensitivity analysis of studies which only used low-osmolar or iso-osmolar contrast and a subgroup analysis of different procedure types, which yielded lower levels of heterogeneity. Second, selection bias may occur as contrast administration could have been avoided in patients with significantly reduced GFR. This effect may be due to the observation that most patients in the included studies had reasonable renal allograft function (eGFR >30 ml/min^{1.73} m²). **In addition, most included studies assessed the incidence of CIAKI in a relatively low risk kidney transplant population. Although several studies have suggested safety of contrast administration in patients with significantly reduced GFR^[29, 37, 38], more studies involving high risk patients are needed to make more definitive conclusions.** Finally, data on the effect of CIAKI on long-term graft function and allograft survival are lacking. Further studies elucidating the impact of the incidence and severity of CIAKI on long-term allograft outcomes will influence clinical management."

Sincerely,

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