## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Pentoxifylline for the prevention of contrast-induced nephropathy: systematic review and meta-analysis of randomized controlled trials |
| **AUTHORS** | Wei, Ling; Zhang, Weizhi; Yang, Yifeng; Li, Dongping |

## VERSION 1 – REVIEW

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| **REVIEWER** | Leehey, David<br>Loyola University Medical Center, Medicine |
| **REVIEW RETURNED** | 21-Aug-2020 |

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| **GENERAL COMMENTS** | The authors have done a meta-analysis of PTX for CIN. The study is well done with few concerns. Under Results, please change "ordinary" patients to a more appropriate tern. Also define "high-risk" patients. Some minor changes in English are needed. |

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| **REVIEWER** | van den Brand, Jan<br>Radboud University |
| **REVIEW RETURNED** | 27-Aug-2020 |

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| **GENERAL COMMENTS** | The manuscript describes a systematic review and meta-analysis of randomized trials on the effect of pentoxifylline (PTX) on the occurrence of contrast induced nephropathy (CIN). The authors searched PubMed, EMBASE and the Cochrane Central Register for Controlled Trial. Out of a total of 109 hits, 36 full texts were assessed, and ultimately 7 included. These 7 studies were all performed in intervention populations (either angioplasty or stenting). The analysis included a total of 740 people with a total of 71 events in the PTX group compared to 744 people with 86 events in the control group, the meta-analyzed odd ratio for CIN was 0.81 with a 95%CI 0.57 to 1.13 in favor of PTX. The secondary outcome, change in serum creatinine, was reported in 4 studies. A single trial (Eshraghi 2018) contributed 98% of the weight to that analysis. The mean difference in change in serum creatinine was -0.02 mg/dl in favor of the PTX group. For reference the normal value of serum creatinine in 0.7 mg/dl and 0.9 md/dl in young healthy women and men respectively. Therefore, this result, while statistically significant, does not appear to be very clinically relevant. The author argue that 'small changes' in serum creatinine may be clinically relevant, and therefore conclude that PTX administration may be a potential agent to prevent CIN.<br><br>In general, the manuscript was well reported. The English needs some revision for choice of words and grammar.<br><br>I have a few questions and suggestions:<br>1. The classification of bias was unclear, high risk was defined as |

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| | high risk of bias in one or more categories or an unclear risk in two or more categories. Low risk meant all categories were classified as low risk. Does this mean that one-and-only-one category 'unclear' risk constitutes a moderate risk?<br>2. The primary outcomes was CIN defined as a 0.5 mg/dl or 25% or greater increase in serum creatinine 48hrs after the procedure. Were other time points (72hrs) accepted? What was accepted the baseline serum creatinine? A usual definition is the minimal value <90 days prior to the intervention.<br>3. Please list (in the appendix) the reason that studies were excluded from the review and analysis.<br>4. What are 'ordinary' patients? Please provide a brief overview of ke variables, such as age, gender, ethnicity, eGFR or serum creatinine, and uACR.<br>5. I would advise against presenting the secondary outcome as a meta-analysis. Essentially, it is a single study that contributes (almost) all the data.<br>6. Most of the included trials did not report randomization procedures. Did the authors consider contacting the corresponding authors to seek more detail information on the study designs and procedures? This concerns only a few quite recent studies, and therefore it should be feasible in my opinion.<br>7. In addition, what other procedures to prevent CIN were taken in the intervention and control groups of the included. Were patients pre-hydrated?<br>8. The authors argue that the _statistically_ significant decrease may be clinically relevant, as other authors reported that 'small' increases in serum creatinine below the threshold for AKI may have clinically important consequences. I feel that this is a misrepresentation of the referenced works. Weisbord et al considered a 0.25 to 0.50 mg/dl increase in serum creatinine small, and the work by Losito considered a 20% increase in serum creatinine. These are still increases more than 10 fold the difference that the authors report.<br>9. The authors claim that the number of CIN events was limited and therefore the renoprotective effect of PTX may be underestimated. I do not quite follow the line of reasoning. Low statistical power results in poor precision (i.e. wide confidence intervals), but not necessarily in underestimation of the parameter estimate.<br>10. The authors argue that (part of) the protective effect of PTX is though the reduction in blood viscosity. This can also be achieved by pre- and posthydration with IV saline or even drinking a few cups of broth at home. I would suggest that the author place their discussion of PTX also in that perspective.<br>11. The authors have not reported information on prevention therapies for CIN in addition to PTX or no-PTX, I would consider lack of this information a limitation as it hampers generalizability.<br>12. The fact that these studies only deal with patients undergoing coronary dilation or stenting and not CABG, CAG without intervention or IV contrast, further limits generalizability.<br>13. I recommend that the authors tone down their conclusion by omitting 'significantly lower Scr increase' and recommend that future trials be adequately powered considering the 5% to 15% event rate. From personal experience and local data, my estimate is that event rates are even lower than 5% in most centers. |

## VERSION 1 – AUTHOR RESPONSE

Reviewer 1: David Leehey, Loyola University Medical Center, USA
The authors have done a meta-analysis of PTX for CIN. The study is well done with few concerns. Under Results, please change "ordinary" patients to a more appropriate tern. Also define "high-risk" patients. Some minor changes in English are needed.

Q1: Under Results, please change "ordinary" patients to a more appropriate tern.
R1: Thank you for your valuable advice. We have made correction according to the Reviewer's comments, and changed "ordinary" patients to "the general population".

Q2: Also define "high-risk" patients.
R2: Thank you for your careful review. Based on the available trials, "high-risk" patients were defined as the population with Mehran score ≥ 11.

Q3: Some minor changes in English are needed.
R3: Thank you for the advice. The manuscript has been polished by an English language editing company.

Reviewer 2: Jan van den Brand, Radboud Institute for Health Sciences, Department of Nephrology, Radboudumc, The Netherlands
The manuscript describes a systematic review and meta-analysis of randomized trials on the effect of pentoxifylline (PTX) on the occurrence of contrast induced nephropathy (CIN). The authors searched PubMed, EMBASE and the Cochrane Central Register for Controlled Trial. Out of a total of 109 hits, 36 full texts were assessed, and ultimately 7 included. These 7 studies were all performed in intervention populations (either angioplasty or stenting). The analysis included a total of 740 people with a total of 71 events in the PTX group compared to 744 people with 86 events in the control group, the meta-analyzed odd ratio for CIN was 0.81 with a 95%CI 0.57 to 1.13 in favor of PTX. The secondary outcome, change in serum creatinine, was reported in 4 studies. A single trial (Eshraghi 2018) contributed 98% of the weight to that analysis. The mean difference in change in serum creatinine was -0.02 mg/dl in favor of the PTX group. For reference the normal value of serum creatinine in 0.7 mg/dl and 0.9 md/dl in young healthy women and men respectively. Therefore, this result, while statistically significant, does not appear to be very clinically relevant. The author argue that 'small changes' in serum creatinine may be clinically relevant, and therefore conclude that PTX administration may be a potential agent to prevent CIN.

Q1: The classification of bias was unclear, high risk was defined as high risk of bias in one or more categories or an unclear risk in two or more categories. Low risk meant all categories were classified as low risk. Does this mean that one-and-only-one category 'unclear' risk constitutes a moderate risk?
R1: According to Cochrane Handbook, The risk of biases are classified into three categories, low risk, unclear risk, and high risk. Low risk meant all categories were classified as low risk. Unclear risk means one category was classified as unclear risk. High risk means high risk of bias in one or more categories or an unclear risk in two or more categories. The manuscript has been modified accordingly.

Q2: The primary outcomes was CIN defined as a 0.5 mg/dl or 25% or greater increase in serum creatinine 48hrs after the procedure. Were other time points (72hrs) accepted? What was accepted the baseline serum creatinine? A usual definition is the minimal value <90 days prior to the intervention.
R2: There are different definitions for CIN according to diagnostic criteria of Acute Kidney Injury Network (AKIN), Risk, Injury, Failure, Loss of kidney function, and End-stage kidney Disease (RFILE)

and KDIGO. The main differences of the definitions were different evaluate time and increasing level of SCr. The definition of CIN in most included studies of this analysis was at least 0.5mg/ or 25% increase in serum creatinine 48hrs after the exposure. Therefore, the definition of CIN was consistent with included studies. The baseline SCr of the included studies was the SCr at the time the participants enrolled. Indeed, the minimal value <90 days prior to the intervention may represent the baseline better, and it should be used in the subsequent studies.

Q3: Please list (in the appendix) the reason that studies were excluded from the review and analysis.
R3: According to the reviewer´s suggestion. We listed the reason that studies were excluded from the review and analysis. There are 21 reviews, 3 case report, 10 animal study, 5 comments, and 45 no relevant studies.

Q4: What are 'ordinary' patients? Please provide a brief overview of ke variables, such as age, gender, ethnicity, eGFR or serum creatinine, and uACR.
R4: Thank for this point. 'ordinary' patients were defined as the population with Mehran score＜11. And as the suggestion of Reviewer 1, we have changed "ordinary" patients to "the general population".

Q5: I would advise against presenting the secondary outcome as a meta-analysis. Essentially, it is a single study that contributes (almost) all the data.
R5: We agree with reviewer that the study report by Eshraghi contributes most data, and we removed this part from the revised manuscript.

Q6: Most of the included trials did not report randomization procedures. Did the authors consider contacting the corresponding authors to seek more detail information on the study designs and procedures? This concerns only a few quite recent studies, and therefore it should be feasible in my opinion.
R6: Thank you for highlighting this point. We have tried to contact the authors and provided feedback on protocol details where possible. In addition, we carefully reviewed available information on Clinical Trials Registry. Finally, data showed that randomization procedures of all included trials were based on computer generated randomization numbers, meaning the randomization procedures were at low risk.

Q7: In addition, what other procedures to prevent CIN were taken in the intervention and control groups of the included. Were patients pre-hydrated?
R7: Thank you for your question. All the enrolled patients were pre-hydrated with normal saline. In addition, Aslanabadi's study used oral 600 mg N-acetyl cysteine twice daily before and after the procedure. We have supplemented the information in the baseline part.

Q8: The authors argue that the _statistically_ significant decrease may be clinically relevant, as other authors reported that 'small' increases in serum creatinine below the threshold for AKI may have clinically important consequences. I feel that this is a misrepresentation of the referenced works. Weisbord et al considered a 0.25 to 0.50 mg/dl increase in serum creatinine small, and the work by Losito considered a 20% increase in serum creatinine. These are still increases more than 10 fold the difference that the authors report.
R8: Thank you for you carefully review. We are very sorry for our negligence. Our results of SCr was the relative value between groups, but not the increase value for each group. However, as the suggestion in Question 5, we agree with reviewer that the study report by Eshraghi contributes most data, and we removed this part from the revised manuscript.

Q9: The authors claim that the number of CIN events was limited and therefore the renoprotective effect of PTX may be underestimated. I do not quite follow the line of reasoning. Low statistical power

results in poor precision (i.e. wide confidence intervals), but not necessarily in underestimation of the parameter estimate.
R9: Thank you for pointing out this. We are sorry that we did not put it exactly that
The reviewer's point is well taken and very convincing (but we didn't make it clear). What we really meant was that low statistical power results in poor precision and the results of these trails should be cautiously interpreted.

Q10: The authors argue that (part of) the protective effect of PTX is though the reduction in blood viscosity. This can also be achieved by pre- and post-hydration with IV saline or even drinking a few cups of broth at home. I would suggest that the author place their discussion of PTX also in that perspective.
R10: Thanks for your suggestion. As reviewer said, pre- and post-hydration with IV saline or even drinking a few cups of broth can also reduce the blood viscosity. And periprocedural hydration maybe the most effective preventive measure for patients at risk of CIN. However, hydration may increase the risk of heart failure, arrhythmia, and short-term mortality in high-risk patients. Therefore, reduction in blood viscosity of PTX should not be ignored.

Q11: The authors have not reported information on prevention therapies for CIN in addition to PTX or no-PTX, I would consider lack of this information a limitation as it hampers generalizability.
R11: Thanks for your comments. Effective prevention strategies and strengthen management are the key to reduce the CIN incidence. Choosing the optimal contrast medium, reducing contrast volume, and personalized hydration are direct and effective strategies to reduce CIN. In addition, remote ischemic preconditioning, N-acetylcysteine and sodium bicarbonate and statins have potential benefits for patients at risk for CIN, but their efficacy needs further study.

Q12: The fact that these studies only deal with patients undergoing coronary dilation or stenting and not CABG, CAG without intervention or IV contrast, further limits generalizability.
R12: Thank you for you carefully review. The dosage of contrast in the coronary dilation or stenting procedures usually more than CAG or IV contrast undergo computerized tomography, resulting in higher incidence of CIN. Evaluating the PTX effect for CIN prevention in this population might be more effective and better economical. But indeed, CAG without intervention, IV contrast and other population exposed to contrast media should be enrolled in the subsequent studies.

Q13: I recommend that the authors tone down their conclusion by omitting ‘significantly lower Scr increase’ and recommend that future trials be adequately powered considering the 5% to 15% event rate. From personal experience and local data, my estimate is that event rates are even lower than 5% in most centers.
R13: It is really true as Associate Editor suggested that we should tone down the conclusions. Current evidence barely strong enough to support the renoprotection of pentoxifylline to contrast-induced nephropathy, and we have modified this conclusion as follow. Perioperative administration of pentoxifylline to patients undergoing angioplasty did not significantly reduce the development of contrast-induced nephropathy, but showed some weak tendency of lower serum creatinine increase. Based on the available trials, the evidence does not support the administration of pentoxifylline for the prevention of contrast-induced nephropathy. If we assume that the CIN incidence in PTX treated group is 8%, and 11% in control group, with a noninferiority limit of 1.5% with power of at least 80% and 1-side type 1 error rate of 2.5%. More than 1000 participants are needed. More trials with larger sample sizes are needed to evaluate the role of pentoxifylline in contrast-induced nephropathy prevention.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Leehey, David<br>Loyola University Medical Center, Medicine |
| **REVIEW RETURNED** | 18-Nov-2020 |

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| **GENERAL COMMENTS** | The authors have responded to my queries. Some English correction (to the additional material) is still needed. |

## VERSION 2 – AUTHOR RESPONSE

Q1: The authors have responded to my queries. Some English correction (to the additional material) is still needed.

R1: Thank you for your thoroughness. The typo errors have been revised in the revised manuscript. In addition, the manuscript has been sent to American Journal Experts to improve the quality of the English throughout the revised manuscript.