Author’s response to reviews

Title: Drugs discontinuation before contrast procedures and the effect on acute kidney injury and other clinical outcomes: a systematic review protocol

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Response to Reviewers:

We thank the editor and reviewer for their helpful comments and suggestions. Below, we reply on a point by point basis to the comments. In brief, we have made the edits and suggestions as advised.

Reviewer reports:

Reviewer #1: This is a well written and timely review examining the evidence for withholding certain medications around the time of contrast injection for the development of AKI. It will greatly serve to inform guidelines regarding CI-AKI. It's timing is important as the composition of IV contrast has changed recently, and previous factors which may have increased the risk of AKI may be different than previously.
I do however have several comments for the authors:

1. While considering RRT as an important outcome, this may not be clinically achievable. You have mentioned that you will be assessing renal outcomes. Is it worth specifying that you will consider specific AKI stage progression (i.e., progression to AKI stage II or III without need of RRT) as an additional outcome?

Authors’ response:

We agree that RRT is an important outcome – but may either be not reported or the numbers might be very small. Hence for renal outcomes, we do consider AKI based on any definition (i.e. the soft CI-AKI definition of 25% or 44 micromol/L rise in creatinine, as well as the AKIN criteria of 50% rise or 26 micromol/L) that the study authors might choose to report. (lines 144 to 151, page 7).

2. As an additional outcome, if NSAIDs are discontinued, would you consider pain or alternative pain regiments as an outcome?

Authors’ response: That is an excellent suggestion to the possible consequences of drug withdrawal – we have added that to line 155 on page 7.

3. Would it be worth conducting an a priori subgroup analysis of outcomes in low and isotonic contrast?

Authors’ response: That is an interesting thought. At present little evidence supports a difference in outcomes between the two, and a priori it is difficult to think of an interaction between the osmolarity of the contrast and the outcomes in this SR. However, we are collecting the type of contrast as a covariate (lines 192-196, page 9), and will examine if any association comes up.

4. Would it be worth conducting an a priori subgroup analysis of cardiac angiography vs. other forms of contrast?

Authors’ response: It is indeed, well known that risk of AKI is different between arterial route (cardiac angiography and other angiography) vs venous route (eg enhanced CT scans). But, as above, it is difficult to expect an interaction between this and the outcome of interest in this SR. We are indeed collecting information on this covariate and examine if any association comes up.

5. Could you provide further detail on the grey literature search?

Authors’ response: We will be searching the grey literature mainly by looking and searching the conference proceedings for the last 3 years in nephrology and cardiology. Research in contrast nephropathy is usually published (and the issue often is a surfeit of papers – not a paucity!).
I think provided the authors can provide answers to the above questions, this article is suitable for publication.

Thank you for the opportunity to review your manuscript.

In addition to the comments raised by the reviewer, the associate editor has raised a few concerns that need consideration.

Background

Pg 4, Lines 85-90 – please provide citations to support comments.

Authors’ response: Thank you for pointing that oversight – we have added citations [7-9] to provide reference for those statements.

Pg 5, Lines 91-93 PRISMA-P requires a clear research question (see Item no 7). Please rephrase broad objectives to specific questions. It is noted that the reported protocol on PROSPERO has clear questions (as does the abstract) and it is therefore surprising that these are not repeated here.

Authors’ response: We did clarify and spell out the exact questions as in the PROSPERO record, now in lines 91-97.

Pg 5-9 The Methods section is wordy and disorganised. Suggest reordering in line with the PRISMA-P structure. Please clarify the comparators: is this simply ‘not withholding’ the drugs that have been listed as being ‘withheld’ in the exposure. Lines 132 – 136 seem to refer to outcomes not comparators. Furthermore, please clarify lines 137-141. Unsure how this is different to what has already been stated.

Authors’ response: Thank you for the suggestion – we have reformatted and re-arranged the section to follow along the PRISMA-P structure, using very similar headings and subheadings.

Pg 8 – Search strategy – will trial registries be searched?

Authors’ response: We do not plan to search trial registries.