Author's response to reviews

Title: Acetylcysteine for prevention of contrast-induced nephropathy after intravascular angiography: A systematic review and meta-analysis.

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Dear Editors:

Regarding: MS: 1057270635047940 - Acetylcysteine for prevention of contrast-induced nephropathy after intravascular angiography: A systematic review and meta-analysis.

Thank you for giving us the opportunity to revise and resubmit this manuscript. We apologize for not directly addressing Dr. Rezkalla’s comments, but it appears that there was a technical problem relating to the PDF file containing the reviewer comments by Shereif H Rezkalla. The file we initially received had no specific comments or questions – thus our response letter indicating that there were specific points that we needed to address. We have now received his comments and address them below.

Reviewer 2 (Shereif H Rezkalla).

We would certainly agree with the reviewer’s general comments in terms of patient preparation for coronary angiography (i.e. clear indications, adequate hydration, minimal volume of contrast media). We would like to add to this list that in patients where several procedures are indicated, consideration should be given to staging the procedures to minimize the total volume of contrast media exposure with any single procedure.

We have reviewed the study by Merten et al (JAMA 2004;291:2328-2334) of sodium bicarbonate for prevention of contrast-induced nephropathy. Although important, the results of the study by Merten et al are not related to the primary objectives of our study. Whether sodium bicarbonate-based hydration and acetylcysteine prophylaxis results in a further reduction in the incidence of contrast-induced nephropathy is speculative and necessitates further study.

The reviewer comments that coronary angiography “without vein grafts can be accomplished with the use of 10 to 20 cc of dye” and “with vein graft angiography and mammary angiography, the amount is higher but certainly should not exceed more than 40 to 50 cc of dye.” These proposed volumes of contrast media appear to contradict the average volume used during studies with acetylcysteine and others such as the study by Merten et al mentioned above. In our meta-analysis of 14 studies, the average volume of contrast media across studies was 145 mL [median 128 mL, interquartile range (IQR) 117-184] and this volume was greater for patients undergoing percutaneous coronary intervention or angioplasty. Perhaps new technology will permit alternatives for patients

The reviewer comments that “the studies that were done with acetylcysteine in this setting were heterogeneous and this is why meta-analysis may be beneficial.” We respectfully disagree with this statement. This is an over-simplification when considering the statistical methods of meta-analysis and can predispose to erroneous conclusions. We draw attention to this problem when referring to the paper by Birck et al on page 12, paragraph 2. Further, on page 7, paragraph 1 and page 13, paragraph 1 we discuss the importance of explaining statistical heterogeneity across studies in terms of validity and interpretation of the results of meta-analyses.

In response to the reviewer’s suggestion that we avoid mention of the historical example of prophylactic magnesium for acute myocardial infarction, we again disagree with the reviewer. We consider this to be an important element of our paper because it clearly demonstrates the possibility of erroneous conclusions made by meta-analyses when there is evidence of statistical heterogeneity and publication bias (as seen here) and how definitive trials (ISIS-4 and MAGIC) were contradictory. Magnesium is no longer recommended as prophylactic therapy in the setting of acute myocardial infarction. However, we agree on replacement of magnesium in the setting of an acute arrhythmia and documented hypomagnesemia. On page 11, paragraph 2 and page 13, paragraph 3 we draw attention to statistical and graphical evidence of potential publication bias of studies of acetylcysteine for prevention of contrast-induced nephropathy.

We will conclude by pointing out that we have not concluded that acetylcysteine is not efficacious for reducing the incidence of contrast-induced nephropathy. We outline on page 13, paragraph 1 and page 15, paragraph 2 that we believe the current literature is inconclusive and that the efficacy of acetylcysteine remains unproven (other recent reviews have made similar global conclusions). We further add that the evidence appears quite promising and that it may now be reasonable to use acetylcysteine in clinical practice. However, a definitive well-designed multi-center trial is needed. Finally, this clinical trial will be most relevant if clinically important endpoints are included (such as mortality as mentioned by the reviewer in paragraph 1), rather than surrogate endpoints based simply on changes in creatinine.

Despite our disagreeing on some points, we thank Dr. Rezkalla for his review and thoughtful comments. We hope that the editors will be satisfied with our response.

We look forward to hearing from you.

Yours sincerely,

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