Incidence of contrast induced nephropathy in patients with renal failure undergoing angiography

Background

Description of the condition

Contrast induced nephropathy (CIN) denotes an impairment of the renal function occurring after percutaneous coronary intervention (PCI) using a contrast agent. CIN is more likely to occur in high risk patients with pre-existing comorbidities like renal failure, diabetes, congestive heart failure and high blood pressure. Patients in end stage renal failure requiring a kidney transplant are likely to experience cardiovascular problems. Cardiovascular disease is the leading cause of morbidity and mortality among end stage renal failure patients before or after kidney transplantation (Lentine et al Circulation. 2012;126:617-663). In the past 10 years guidelines on how to manage cardiovascular disease in kidney transplant patients have changed, particularly due to the risk of CIN occurring at the time of invasive investigations. Currently the latest guidance (2012) only recommends non-invasive stress testing for asymptomatic patients that are at high risk of concomitant cardiovascular disease. In high risk patients who are undergoing procedures using contrast agents, a number of pharmacological interventions have been proposed to reduce the risk of CIN. However, their use remains controversial. The aim of this review is two fold: to establish the incidence of CIN in patients with pre-existing renal failure who undergo angiography/PCI with a contrast agent, and to establish the efficacy of pharmacological strategies which may reduce the incidence of CIN.

Description of the intervention

Coronary angiography, also known as cardiac catheterisation, allows investigation of disease of the artery through a special X-ray obtained with a contrast dye. Patients undergoing angiography/cardiac catheterisation with a contrast dye/medium are likely to elicit nephropathy because of the contrast medium. This review will investigate the incidence of CIN.

Secondly, we will be assessing the effectiveness of the following pharmacological strategies for reducing incidence of CIN in high risk patients undergoing coronary angiograms. These strategies are: Acetylcysteine, nicorandil, bicarbonates, thioctic acid, statins, amiodipine, ebselen, fenoldopam, anisodamine, theophylline, pentoxifylline and trimetazidine.

Why it is important to do this review

The risk of CIN after coronary angiography in patients with end stage renal failure has not been evaluated in prospective studies with a large number of patients and control groups (Lentine et al Circulation. 2012;126:617-663). The current most up to date guidelines recommend that patients in end stage renal failure should, whenever possible, undergo transplantation before managing their coronary artery disease (CAD). This is to reduce the risk of invasive investigations done through a contrast medium which are necessary before CABG. Hammersmith Hospital receives a large number of referral of patients in end stage renal failure needing CAD management. Currently, despite the guidelines, the majority of these patients are referred by the cardiologists to resolve the CAD before the transplantation. This entails investigation through angiography and maybe cardiac catheterisation. These patients seem to be faring well in the outcome of treatment of CAD, and then go on to receive transplantation when the organ is available.
Resolving the uncertainty around the risk of CIN after coronary angiography in patients with end stage renal failure is a first step in understanding if some patients could benefit from having their CAD treated before the kidney transplant.

The efficacy of pharmacological interventions such as N-acetylcysteine (NAC) compared to hydration alone is uncertain especially in patients at high-risk of developing CI-AKI; international guidelines recommend not using NAC for renoprotection in such patients due to a lack of evidence. Given the risk of CI-AKI in high-risk patients, it is important to estimate the efficacy of currently-used pharmacological agents to prevent CI-AKI.

**Objective**

To quantify the incidence of CIN in patients with pre-existing renal failure who undergo angiography using a contrast agent. To establish the efficacy of proposed pharmacological strategies to reduce the incidence of CIN in high risk renal patients.

**Methods**

**Criteria for considering studies for this review**

**Types of studies**

We will include all published and unpublished randomised controlled trials (RCTs), phase I, phase II, phase III, phase IV clinical trials, comparative studies, controlled clinical trials, evaluation studies, meta analyses, "review" or systematic reviews.

**Types of participants**

Men or women (18 years or older) with pre-existing renal failure undergoing coronary angiography. The control group had no intervention to ameliorate kidney dysfunction other than hydration.

**Types of interventions**

We are not investigating an intervention.

**Types of outcome measures**

**Primary outcome**

- Incidence of CIN.

**Secondary outcomes**

- Death
- Need for dialysis
- MACE
- IC unit length of stay
**Search methods for identification of studies**

We will restrict the searches to English language, studies on human, between 1990 and 2016 No publication status restriction.

**Electronic searches**

We will search the following electronic databases: Ovid Medline, Embase and the Cochrane Library.

The following search strategy will be used to search Ovid MEDLINE(R) and adapted as appropriate for the other databases.

1. exp Acetylcysteine/
2. exp Nicorandil/
3. exp Bicarbonates/
4. exp Thioctic Acid/
5. exp Anticholesteremic Agents/ or exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or statin.mp. or exp Pravastatin/ or exp Lovastatin/
6. exp Amlodipine/
7. ebselen.mp.
8. exp Fenoldopam/
9. anisodamine.mp.
10. exp Theophylline/
11. exp Pentoxifylline/
12. exp Trimetazidine/
13. exp Ascorbic Acid/
14. exp Acute Kidney Injury/
15. Cardiac Catheterization/ae [Adverse Effects] (Including Related Terms)
16. Contrast Media/ae [Adverse Effects] (Including Related Terms)
17. (contrast adj3 nephro*).ab.ti.
18. Coronary Angiography/
19. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
20. 14 or 15 or 16 or 17
21. 18 and 19 and 20
22. limit 21 to yr="1990 -Current"
23. limit 22 to (english language and humans and (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or randomized controlled trial or "review" or systematic reviews))

**Searching other resources**

We will search the reference lists of all included studies and relevant published reviews. We will also contact experts in the field and trial authors for further information or unpublished data.

**Data collection and analysis**

The data collection will be carried out by two of the review authors, FF and AS. The data analyses will be conducted by three of the review authors, FF, AS and BR.

**Selection of studies**

Two review authors (FF and AS) will independently assess for inclusion the full text papers of all the studies identified as potentially eligible by screening. Any disagreements will be resolved by discussion with a third review author (BR). Duplicate publications will be excluded. The study selection process will be presented in a PRISMA flow diagram.
Data extraction and management

Two review authors (FF and AS) will independently extract data from all included studies. Disagreements will be resolved through discussion and consensus with a third review author (BR). We plan to extract the following information/data from each study:

1. **Publication details** (authors, title, date of publication, language, country of origin)
2. **Study characteristics** (setting (single centre or multicentre), study design, if RCT: method of randomisation (sequence generation, concealment of allocation), blinding of outcomes, number of patients randomised to each group, sample size calculation, if performed. If prospective controlled: number of patients)
3. **Participant characteristics** (inclusion and exclusion criteria, demographics, clinical characteristics (e.g. extent of disease, presence of co-morbidities), baseline characteristics)
4. **Angiography characteristics** (type of contrast)
5. **Outcomes** (as detailed in previous section). We will record the number of participants assessed for each outcome, mean values and standard deviations (if available), or medians and interquartile ranges, for continuous data, number of events in each group for dichotomous data, and any reported summary statistics (e.g. incidence estimates, confidence intervals (CI), standard errors (SE), ranges).

We will contact the trial authors for information if any of the above data items are missing. AS will input the data on the database and FF will be responsible for checking the data entered.

Assessment of risk of bias in included studies

Two review authors (FF and AS) will independently assess the risk of bias in each included study. Disagreements will be resolved by discussion with a third review author (BR).

We will assess the following domains as low risk of bias, unclear or high risk of bias.

1. Generation of allocation sequence (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants, personnel and outcome assessors (performance bias)
4. Incomplete outcome data (attrition bias)
5. Selective reporting (reporting bias)
6. Other sources (e.g. presentation data bias, sampling bias, sponsorship bias)

Quality of evidence on CIN and adverse effects

We will extract information from included studies about incidence of CIN and other adverse effects that researchers suspect were related to the angiography/PCI. We will assess the quality of evidence.

Outcome Measures
**Dichotomous data**

We will calculate risk ratios (RRs) and 95% confidence intervals (CIs) for the following dichotomous outcomes: Incidence of CIN; death; MACE; need for renal dialysis; adverse effects.

**Continuous data**

For continuous outcomes, we will calculate mean differences (MD) and 95% confidence intervals when the same scale is used to measure an outcome across separate studies, or standardised mean differences (SMD) and 95% confidence intervals if results are reported using different scales or different versions of the same scale. Length of hospital stay or IC length of stay is, strictly, time-to-event data. If authors report medians and inter-quartile ranges for length of IC or hospital stay, we will calculate hazard ratios (HR) and 95% confidence intervals (allowing for censoring). Care will be taken to assess the risk of bias from selective attrition.

**Unit of analysis issues**

We do not anticipate that there will be any unusual study designs (e.g. cluster-randomized trials). We will avoid double-counting of participants where there are multiple interventions in the same trial.

**Dealing with missing data**

We will contact trial authors for important variables that were not reported in the papers or missing statistics. However our main analyses will be based on participants who completed the trial but we will perform sensitivity analysis for worst and best case scenarios and discuss the potential impact of these on the findings of the review in the discussion section.

**Assessment of heterogeneity**

We will assess clinical heterogeneity across studies by examining details of participants, baseline data, interventions and outcomes to determine whether studies are similar. We will quantify statistical heterogeneity using the $I^2$ statistic; we will consider there to be a high level of statistical heterogeneity if $I^2 > 50\%$ (Higgins and Green, 2011). We will attempt to explain any observed clinical or statistical heterogeneity in the results of the review.

**Assessment of reporting biases**

We will use funnel-plots to assess reporting bias at study level (publication bias). Selective outcome reporting will be assessed as part of the domain-based assessment of the risk of bias to included studies.

**Data synthesis**

We will summarize trial findings using forest plots and meta analysis. We will summarise included studies in narrative forms if we do not find trials that are sufficiently similar to justify a meta-analysis.

**Sensitivity analysis**

We plan to conduct sensitivity analyses to explore the robustness of results by comparing the results of fixed- and random-effects meta-analyses. We will conduct sensitivity analysis restricted to published trials.