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Contrast-Induced Nephropathy: Comparative Effects of Different Contrast Media

Executive Summary

Background

The administration of iodinated contrast media is an essential component of many diagnostic and therapeutic procedures that involve radiologic imaging. An important potential side effect of iodinated contrast administration is contrast-induced nephropathy (CIN), defined as an increase in serum creatinine of more than 25 percent or 0.5 mg/dL within 3 days of intravascular administration of contrast media in the absence of an alternative etiology.¹

The precise mechanism of CIN is not entirely understood. The leading theories are that CIN results from hypoxic injury of the renal tubules induced by renal vasoconstriction or by direct cytotoxic effects of contrast media.^{2,3} Alternatively, some experts have argued that acute kidney injury occurring after intravascular administration of contrast media is caused instead by coexisting risk factors and is only coincidentally related to the contrast media, especially if contrast media are administered intravenously.⁴ Regardless of the precise etiology, however, the development of acute kidney injury after use of intravascular contrast media remains a major concern for clinicians.

Osmolality of contrast media is a key factor determining its tolerability.⁵ Since the 1990s, low-osmolar contrast media (LOCM; 2–3 times plasma osmolality) has

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been the standard of care for intravascular injection. The newest class of intravascular contrast, iso-osmolar contrast media (IOCM), is isotonic to plasma. Iodixanol is currently the only IOCM available for intravascular injection. A preliminary literature search revealed conflicting



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reports about whether IOCM is associated with a reduction in CIN risk compared with LOCM.

In this systematic review, we sought to determine the comparative effects of different types of intravascular contrast media in patients receiving imaging studies or undergoing image-guided procedures. The preliminary search also revealed reports that intra-arterial administration may be associated with a greater CIN risk than intravenous administration, and therefore we also investigated whether the effects vary according to route of contrast administration.^{4, 6, 7}

The populations of interest included patients of all ages and levels of risk for CIN. The interventions and comparisons of interest included contrast type (IOCM or LOCM) and administered dose or volume. The main outcome was the development of CIN. Secondary outcomes were also considered, such as need for renal replacement therapy (including dialysis or hemofiltration), cardiac outcomes, adverse events, mortality, imaging quality, and diagnostic accuracy. We sought evidence from both short- and long-term studies, and we considered both inpatient and outpatient settings.

Key Question

Key Question: What are the comparative benefits and harms of different contrast media in patients receiving imaging studies requiring intravenous or intra-arterial administration?

- a. How do benefits or harms of contrast media differ by patient characteristics (known risk factors such as age, comorbidity, glomerular filtration rate, or creatinine clearance)? How do benefits or harms differ by the dose of contrast medium (i.e., by volume of dose and number of doses)?
- b. How do benefits or harms of contrast media differ according to the type of preventive strategy used?

Data Sources

We searched the following databases for primary studies published through October 1, 2014: MEDLINE®, EMBASE®, and the Cochrane Library. In addition, we looked for conference proceedings and other reports by searching the Scopus database. We reviewed the reference lists of relevant articles and related systematic reviews to identify original journal articles and other reports the database searches might have missed. We also searched ClinicalTrials.gov to identify ongoing studies. Additionally, we requested data from the manufacturers

of contrast media, and searched the U.S. Food and Drug Administration Adverse Event Reporting System (AERS).

Study Eligibility Criteria, Participants, and Interventions

We followed the PICOTS framework (population, interventions, comparisons, outcomes, timing, and setting) in developing the criteria for including studies in the review, and we included studies of patients of all ages with low, moderate, or high risk of developing CIN. We included randomized controlled trials (RCTs) in which the intervention group received intra-arterial or intravenous injection of IOCM or LOCM. We also reviewed applicable observational studies. Studies had to report on impairment of renal function before and after (up to 72 hours) contrast injection to be included in the report. For studies reporting on CIN (as defined above), we also extracted data on cardiac outcomes, need for renal replacement therapy, mortality, length of hospital stay, adverse events, imaging quality, and diagnostic accuracy.

Study Appraisal and Synthesis Methods

The titles and abstracts were screened independently by two reviewers. When reviewing abstracts followed by the full text of articles, both reviewers had to agree on inclusion or exclusion. Disagreements that could not be resolved by the two reviewers were resolved by a third expert member of the team. At random intervals during screening, quality checks were performed to ensure that eligibility criteria were applied consistently.

We reviewed primary studies, as defined by our inclusion criteria, and we performed de novo meta-analyses of all studies on a given comparison if study heterogeneity was not important by clinical, qualitative, and statistical criteria. Pooled risks were calculated using a random-effects model using the DerSimonian and Laird method.⁸

Two reviewers independently assessed each study's risk of bias using five items from the Cochrane Risk of Bias tool for randomized studies:⁹

Was the allocation sequence adequately generated?

Was allocation adequately concealed?

Was knowledge of the allocated intervention adequately prevented during the study?

Were incomplete outcome data adequately addressed?

Are reports of the study free of suggestion of selective outcome reporting?

When assessing the risk of bias in each study, we focused on the main outcome of interest, CIN, an outcome that is objectively measured by laboratory testing. When applicable, we graded other outcomes independently.

The team graded the strength of evidence (SOE) on comparisons of interest for the key outcomes. We used the grading scheme recommended in the Agency for Healthcare Research and Quality “Methods Guide for Effectiveness and Comparative Effectiveness Reviews”¹⁰ and considered all domains: study limitations, directness, consistency, precision, reporting bias, and magnitude of effect.

A body of evidence was assessed as having high study limitations if greater than 50 percent of the studies scored negative in one or more of the risk-of-bias criteria. A body of evidence was assessed as having low study limitations if most (51% or greater) of the studies scored positive in all five domains. Bodies of evidence not meeting one of the above criteria were assessed as having medium study limitations.

Following the guidance of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group,¹¹ we rated evidence as precise if the total number of patients exceeded the optimum information size and the 95% confidence interval (CI) excluded a risk ratio of 1.0. If the total number of patients exceeded the optimum information size and the 95% CI did not exclude the possibility of no difference (i.e., risk ratio of 1.0), we rated the evidence as precise only if the 95% CI excluded the possibility of a clinically important benefit or harm (i.e., risk ratio less than 0.75 or greater than 1.25). For the main outcome of interest, CIN, we used an optimum information size of 2,000, based on an expected 0.1 probability of CIN in the comparison group and a minimally important relative difference of 25 percent. For less frequent adverse outcomes, we used an optimum information size of 10,000, based on an expected 0.02 probability in the comparison group and a minimally important relative difference of 25 percent. If only one study was available for a given comparison, we downgraded the evidence for having unknown consistency. We classified the SOE pertaining to each comparison into four category grades: high, moderate, low, and insufficient. The body of evidence was considered high grade if study limitations were low and there were no problems in any of the other domains, and subsequently downgraded for each domain in which a problem was identified. If the magnitude of effect was very large, the SOE could be upgraded.

Observational studies were considered in grading the strength of a body of evidence if the overall results of the observational studies were not similar to results of the RCTs applicable to the comparison.

Results

The literature search revealed 29 RCTs for summary and analysis and 10 observational studies. Five RCTs compared two or more LOCMs in 826 patients.¹²⁻¹⁶ Twenty-five RCTs compared IOCM with one or more LOCMs in 5,053 patients.^{12, 17-40} Included in these RCTs was one study that reported data on both types of comparisons.¹² In the five RCTs comparing LOCM versus LOCM, four studies had a problem with one or more of the five risk-of-bias items that we assessed. In the 25 RCTs comparing IOCM versus LOCM, all studies had a problem with one or more of the five risk-of-bias items that we assessed. We did not find any studies that examined whether the benefits or harms of contrast media differed according to the type of strategy used to prevent CIN.

No study comparing one LOCM with another LOCM reported a statistically significant or clinically important difference between study arms in the incidence of CIN (or related measures of a change in renal function), and the overall analysis did not suggest that any one LOCM was superior to another (low SOE). RCTs comparing LOCM versus LOCM did not report outcomes similarly enough to be combined numerically. No studies indicated that a difference existed for a selected subgroup of patients or for a given dose of contrast media.

We found a borderline statistically significant reduction in short-term CIN risk (less than 7 days after administration of contrast) with IOCM compared with a diverse group of LOCMs (pooled relative risk, 0.80; 95% CI, 0.65 to 0.99, $p=0.045$; moderate SOE). However, the reduction was too small to be clinically important. When the analysis was stratified by route of administration, the pooled risk ratio was 0.80 (95% CI, 0.64 to 1.01) for intra-arterial and 0.85 (95% CI, 0.42 to 1.71) for intravenous, suggesting no difference in comparative CIN risk by route of administration. The SOE was low to support no clinically important difference between IOCM and LOCMs with regard to need for renal replacement therapy (5 studies), cardiovascular outcomes (7 studies), mortality (8 studies), adverse events (12 studies), or image and diagnostic quality (2 studies). We did not see any definitive evidence of a difference in CIN incidence between IOCM and LOCM that varied according to patient characteristics or contrast dose.

Results of the 10 observational studies in our review were similar to those reported in the RCTs. We did not make any changes in the SOE grading based on the observational studies.

Discussion

In this systematic review, the small number of trials comparing one LOCM with another LOCM reported no statistically significant or clinically important differences in the risk of CIN. For the trials comparing IOCM with LOCM, we found a slight reduction in CIN risk for IOCM that was of borderline statistical significance. However, the point estimate of this reduction did not exceed a minimally important relative risk difference of 25 percent.

Most trials in our review involved patients receiving intra-arterial contrast. In the few trials involving intravenous contrast, we saw no evidence that the relationship between contrast type and CIN risk differed from that observed in the intra-arterial trials.

We found no difference between LOCM types or between LOCM and IOCM in potential sequelae of CIN, such as cardiovascular events, mortality, need for renal replacement therapy, or other adverse events. Because we excluded studies that did not report data on CIN, we excluded studies that reported only nonrenal outcomes. However, a recent meta-analysis of RCTs comparing IOCM and LOCM that included such studies found no conclusive evidence that IOCM is superior to LOCM with respect to cardiovascular events.⁴¹ This supports the findings from our dataset, which focused on renal outcomes.

Our results are similar to results of three published meta-analyses, which reported no statistically significant reduction of CIN with IOCM compared with LOCM.⁴²⁻⁴⁴ Even though our review included six RCTs that have been published since those three meta-analyses, we obtained a similar estimate of the relative risk. Five other systematic reviews reported a lower incidence of CIN with IOCM than with LOCM, but all had important limitations and included different sets of studies than our review.⁴⁵⁻⁴⁹ In one of these meta-analyses,⁴⁵ the two studies favoring IOCM the greatest^{50,51} were excluded from our analysis because CIN was not adequately defined. Two other systematic reviews made indirect comparisons of contrast agents^{46, 47} and reported differences between IOCM and the LOCM iohexol, but not with other LOCMs. However, one of the indirect comparison studies was a network analysis that pooled all outcomes (not just CIN),⁴⁶ and the other indirect comparison study included observational data (not just RCTs).⁴⁷ One of the reviews included only trials of IOCM

that were sponsored by its manufacturer,⁴⁸ and another meta-analysis⁴⁹ included a large unpublished positive trial comparing IOCM with iopromide. Data for this trial are available only in a 2010 meeting abstract; to date, the study has not been published.

It should be noted that our review addressed a clinical comparison involving contrast media and did not seek to review evidence concerning the pathophysiology, causal pathway, or epidemiology of CIN. The precise mechanism of CIN is not entirely understood. Some evidence exists from propensity-score-matched retrospective studies questioning the strength of the relationship between contrast administration and CIN.⁴ This relationship is important for designing future research but does not affect the conclusions of this review regarding the comparative impact of contrast media type on observed CIN.^{4, 7, 52}

Several limitations of the review should be noted. We generally considered LOCM agents together as a group even though seven different LOCM chemical compounds were used in the studies we reviewed. While direct comparisons of LOCMs are sparse, indirect evidence suggests that iohexol may differ from other LOCMs. The greatest CIN reduction with IOCM was reported in a study comparing it with iohexol.³⁷ Two indirect comparisons also suggested that differences existed between iohexol and other LOCMs.^{46, 47} These comparisons were not compelling. As mentioned above, one study was a network meta-analysis that pooled all outcomes without focusing on a homogeneous body of studies using a similar definition of the main outcome of interest. The other study was designed to assess other comparisons, such as N-acetylcysteine versus intravenous saline, and the IOCM versus LOCM comparison was a secondary analysis.

We found that studies examining the risk of CIN with different types of contrast media generally provided little detail about clinical indications for the diagnostic or therapeutic procedures, or other clinical details such as the severity of renal impairment. As a result, we were not able to assess whether the comparisons between types of contrast media depended on the indications for use of contrast media or baseline renal function. Furthermore, the studies frequently omitted details about total contrast volume, length of procedure, and contrast injection rates. These are potential sources of heterogeneity among the studies. Based on our inclusion criteria, we did not select studies based on these characteristics, so the results likely apply to a relatively diverse population of patients and procedures. We suggest that future research focus on identifying clinical factors that may be associated with a benefit of IOCM compared with LOCM.

Conclusions

In summary, we found low SOE to support no differences in CIN risk between LOCMs and moderate SOE that IOCM had a slightly lower risk of CIN than LOCM, but the lower risk was not clinically important and had only borderline statistical significance. No relationship was found between comparative CIN risk and route of administration. For clinicians, these findings suggest that the choice between IOCM and LOCMs will not have an important effect on the risk of CIN.

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Full Report

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