Comparative Effectiveness Review
Number 155

Effective Health Care Program

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.²³ 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 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
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” 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. 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. 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. In one of these meta-analyses, the two studies favoring IOCM were excluded from our analysis because CIN was not adequately defined. Two other systematic reviews made indirect comparisons of contrast agents 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), and the other indirect comparison study included observational data (not just RCTs). One of the reviews included only trials of IOCM that were sponsored by its manufacturer, and another meta-analysis 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. 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.

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. Two indirect comparisons also suggested that differences existed between iohexol and other LOCMs. 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.

References


Full Report
Comparative Effectiveness Review
Number 156

Contrast-Induced Nephropathy: Comparative Effectiveness of Preventive Measures

Executive Summary

Background
The administration of iodinated contrast media is an essential component of many diagnostic and therapeutic procedures that involve radiologic imaging. One 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.\(^1\) This definition of CIN is the one most commonly used in the past in studies examining the risk, prevention, and treatment of CIN. More recent definitions of acute kidney injury have not yet been used extensively in the CIN literature.

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 the contrast media.\(^2\,^3\) Some experts have questioned whether acute kidney injury occurring after intravascular administration of contrast media is caused by coexisting risk factors and 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.

Effective Health Care Program
The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).

Clinicians often worry about the possibility that intravascular administration of contrast media could lead to acute or chronic kidney failure. The reported incidence of CIN varies, but it is a leading cause of hospital-acquired kidney failure.\(^5\) Although renal function returns to normal
in most patients, the acute kidney injury may require renal replacement therapy or lead to chronic kidney disease (CKD) in a small proportion of patients who develop CIN. Because of increasing use of contrast media in radiologic and cardiologic procedures, and the increasing prevalence of populations vulnerable to CIN (i.e., people having CKD, diabetes mellitus, or hypertension, as well as the elderly), kidney failure due to CIN is a substantial concern.

Numerous strategies have been used to try to prevent CIN. These strategies include oral hydration; volume expansion with sodium chloride or bicarbonate or a combination of both; administration of N-acetylcysteine; withdrawal of metformin, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or nonsteroidal anti-inflammatory drugs; hemofiltration or hemodialysis; statins; use of low-osmolar or iso-osmolar nonionic contrast media; and reducing the volume of contrast media administered. Despite these varied strategies, no clear consensus exists in clinical practice about the most effective intervention to prevent or reduce CIN. We therefore sought to perform a comprehensive systematic review of the effectiveness of different measures for preventing CIN.

We also sought to determine whether the risk of CIN, and therefore the need for preventive measures, varies according to route of administration, type of contrast media, or patient characteristics. Intra-arterial procedures are thought to carry the highest risk of CIN, and therefore most of the studies are in the population undergoing these procedures, while the need for preventive strategies for patients undergoing intravenous procedures is more controversial. To better understand the results, we separately analyze patients who received intravenous versus intra-arterial contrast media, as these groups may have different risk profiles and susceptibility to CIN. We also performed a separate analysis for patients receiving iso-osmolar contrast media (IOCM) or low-osmolar contrast media (LOCM), the two types of contrast media in regular clinical use today in the United States. Finally, preventive measures may be more effective in patients at higher risk of CIN, so we analyzed data by baseline risk when possible.

Key Question

Key Question: In patients undergoing imaging studies requiring intravenous or intra-arterial contrast media, what is the comparative effectiveness of interventions to prevent contrast-induced nephropathy for the outcomes of incidence of contrast-induced nephropathy, chronic kidney disease, end stage renal disease, mortality, and other adverse events?

a. How does the comparative effectiveness of prevention measures vary by patient characteristics (known risk factors such as age, comorbidity, glomerular filtration rate, or creatinine level)?

b. How does the comparative effectiveness of prevention measures vary according to the type of contrast media used (i.e., low-osmolar contrast media vs. iso-osmolar contrast media)?

c. How does the comparative effectiveness of prevention measures vary by characteristics of the interventions (e.g., dose, duration, and timing)?

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. We searched for publicly available data held by the U.S. Food and Drug Administration.

Study Eligibility Criteria, Participants, and Interventions

We followed the population, interventions, comparators, outcomes, timing, and setting (PICOTS) framework in developing the criteria for including studies in the review, and included studies of patients of all ages with low, moderate, or high risk of developing CIN. We included randomized controlled trials (RCTs) of any intervention to prevent CIN (including administration of N-acetylcysteine, sodium bicarbonate solution, sodium chloride solution, statins, adenosine antagonists, diuretics, vasoactive drugs, antioxidants, dopamine, and renal replacement therapy) in which the study groups received either IOCM or LOCM via intravenous or intra-arterial injection. Studies had to report on at least one of the outcomes listed in the Key Question. We included observational studies where available for all comparisons of interest.
Study Appraisal and Synthesis Methods

The titles and abstracts were independently screened by two reviewers. Inclusion at the title-screening level was liberal; if a single reviewer believed an article might contain relevant information, the article was moved to the abstract level for further screening. 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, senior team members performed quality checks to ensure that eligibility criteria were applied consistently.

We performed de novo meta-analyses of all studies on a given comparison if the studies were similar by qualitative or statistical criteria. Pooled risks were calculated using a random-effects model using the method of DerSimonian and Laird. Statistical heterogeneity was assessed using the I-squared statistic.

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

- 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, we focused on the main outcome of interest, CIN, an outcome that is objectively measured by laboratory testing. Study limitations were determined for each comparison group for CIN and other reported outcomes. Study limitations were determined using the following algorithm for a body of evidence. 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 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.

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” and considered all domains: study limitations, directness, consistency, precision, reporting bias, and magnitude of effect.

Following the guidance of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group, we rated evidence as precise if the total number of patients exceeded an 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 risk 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 risk 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. 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 the RCTs applicable to the comparison.

Organization of This Report

The following Results section reports on a number of comparisons. We report in detail on comparisons for which substantial evidence exists, starting with the comparisons that have received the most attention in the literature (N-acetylcysteine plus intravenous saline vs. intravenous saline, intravenous sodium bicarbonate vs. intravenous saline, N-acetylcysteine plus intravenous saline vs. intravenous sodium bicarbonate, statins plus intravenous saline vs. intravenous saline, adenosine antagonists plus intravenous saline vs. intravenous saline, renal...
replacement therapy vs. intravenous saline, and ascorbic acid plus intravenous saline vs. intravenous saline). At the end of the results section, we refer to information about other miscellaneous comparisons for which there were too few studies to draw any conclusions. Details on those comparisons appear in Appendixes H and I of the full report.

Results

The literature search revealed a total of 177 articles: 154 RCTs and 23 observational studies on interventions for preventing CIN, including 65 RCTs (N = 12,990) on N-acetylcysteine versus intravenous saline; 27 RCTs (N = 3,398) on intravenous sodium bicarbonate versus intravenous saline; 6 RCTs (N = 1,519) on N-acetylcysteine versus sodium bicarbonate; 14 RCTs (N = 6,188) on statins (4 comparing a statin to intravenous saline, 4 comparing a statin plus N-acetylcysteine to N-acetylcysteine, and 6 other comparisons of statin versus statin, statin by dose, or statins plus other agents); 5 RCTs (N = 3,647) on adenosine antagonists; 6 RCTs (N = 790) on use of hemodialysis or hemofiltration to prevent CIN; and 8 RCTs (N = 2,026) comparing ascorbic acid to intravenous saline or N-acetylcysteine.

We included in the meta-analyses 53 RCTs investigating N-acetylcysteine with intravenous saline versus intravenous saline with or without a placebo (45 studies using only intra-arterial contrast media, 7 studies using intravenous contrast media, and 1 study that did not report the route of administration); 18 RCTs investigating the use of sodium bicarbonate versus intravenous saline (13 studies using only intra-arterial contrast media, 2 studies using only intravenous contrast media, and 3 studies using either intra-arterial or intravenous contrast media); 4 RCTs investigating use of intravenous sodium bicarbonate versus N-acetylcysteine plus intravenous saline (3 studies using intra-arterial contrast media and 1 study using intravenous contrast media); 4 RCTs investigating use of a statin versus a placebo or intravenous saline (all studies using intra-arterial contrast media); 4 RCTs investigating the use of a statin plus N-acetylcysteine versus N-acetylcysteine alone (all studies using intra-arterial contrast media); 3 RCTs investigating use of hemodialysis versus intravenous saline alone (all studies using intra-arterial contrast media, 1 of which also included some patients receiving intravenous contrast media); 4 RCTs investigating use of an adenosine antagonist with intravenous saline versus intravenous saline alone (3 studies using intra-arterial contrast media and 1 study using intravenous contrast media); 6 studies investigating the use of ascorbic acid versus intravenous saline (all studies using intra-arterial contrast media); and 3 studies investigating the use of ascorbic acid versus N-acetylcysteine (all studies using intra-arterial contrast media). The results of these studies were published between 1998 and 2014.

N-Acetylcysteine Versus Intravenous Saline

Using a random-effects model to pool studies comparing N-acetylcysteine with intravenous saline versus intravenous saline with or without a placebo, the pooled risk ratio for CIN was 0.81 (95% CI, 0.63 to 1.04) for high-dose N-acetylcysteine (>1,200 mg/day), indicating a small effect that is clinically unimportant and statistically insignificant with low SOE, and 0.77 (95% CI, 0.66 to 0.90) for low-dose N-acetylcysteine (1,200 mg/day or less), indicating a small clinically unimportant effect. Sensitivity analyses revealed imprecise estimates of the pooled risk ratio for CIN when stratified by route of administration of contrast media: 0.82 (95% CI, 0.63 to 1.06) for high-dose N-acetylcysteine when intra-arterial contrast media were used; 0.60 (95% CI, 0.15 to 2.44) for high-dose N-acetylcysteine when intravenous contrast media were used; 0.77 (95% CI, 0.66 to 0.91) for low-dose N-acetylcysteine when intra-arterial contrast media were used; and 0.68 (95% CI, 0.34 to 1.37) for low-dose N-acetylcysteine when intravenous contrast media were used. The pooled risk ratio was 0.74 (95% CI, 0.63 to 0.88) for N-acetylcysteine when LOCM was used, suggesting a clinically important benefit, and 1.06 (95% CI, 0.81 to 1.38) for N-acetylcysteine when IOCM was used. When we examined how the risk ratio estimates varied according to baseline characteristics of the study population, we did not observe any meaningful difference by age, baseline renal function, presence or absence of diabetes mellitus, or proportion of female patients. When we examined how results of studies of N-acetylcysteine varied in forest plots organized by the number of study limitations, we did not see any pattern indicative of a trend by study quality.

The SOE was low that N-acetylcysteine with intravenous saline did not differ from intravenous saline with or without a placebo in the need for renal replacement therapy, cardiac events, or length of hospitalization. Most of the studies addressing these outcomes had important study limitations (frequently lacking documentation of allocation concealment or blinding of participants and personnel) and were consistent but imprecise. We found insufficient evidence to draw conclusions about the effect of N-acetylcysteine on mortality. The results of observational studies were similar to the RCTs.
**Intravenous Sodium Bicarbonate Versus Intravenous Saline**

In studies comparing intravenous sodium bicarbonate versus intravenous saline, the overall pooled risk ratio of CIN was 0.90 (95% CI, 0.69 to 1.18). The point estimate of the risk ratio indicated a clinically unimportant difference in the risk of CIN. The associated CI ruled out a clinically important increase in CIN but did not rule out the possibility of a clinically important decrease in CIN. However, intravenous sodium bicarbonate was more effective than intravenous saline in preventing CIN (pooled risk ratio, 0.62; 95% CI, 0.40 to 0.95), with a clinically important benefit when given for studies with LOCM only, but not when given for studies with IOCM (pooled risk ratio, 1.00; 95% CI, 0.77 to 1.29). The SOE was low for this conclusion because most of the studies had important study limitations (frequently lacking documentation of allocation concealment or blinding of participants and personnel) and inconsistent results.

The SOE also was low that intravenous sodium bicarbonate did not differ from intravenous saline in mortality or the need for renal replacement therapy. Most of the studies addressing these outcomes had at least one important study limitation (frequently lacking blinding of participants and personnel) and were consistent but imprecise. We found insufficient evidence to draw conclusions about how intravenous sodium bicarbonate compared with intravenous saline in the risk of cardiac events and length of hospitalization. Two observational studies reported a beneficial effect of sodium bicarbonate in reducing CIN.

**N-Acetylcysteine Versus Sodium Bicarbonate**

In the RCTs comparing intravenous sodium bicarbonate with the combination of N-acetylcysteine and intravenous normal saline, the pooled risk ratio for CIN was 0.92, indicating no clinically important difference. However, the studies were inconsistent and the 95% CI was so wide (0.60 to 1.42) that we cannot rule out the possibility of either an important decrease or important increase in risk of CIN. Therefore, the SOE was insufficient to support a conclusion about the comparative effectiveness of these two interventions. The evidence also was insufficient to draw conclusions about potential differences between the two interventions in mortality, cardiac events, need for renal replacement therapy, or length of hospitalization. Two observational studies compared N-acetylcysteine to sodium bicarbonate. One showed no difference between interventions, and the other showed a higher incidence of CIN in patients receiving sodium bicarbonate alone.

**Statins**

The SOE was moderate in studies that compared use of a statin plus intravenous fluids versus intravenous fluids alone, showing a clinically important and statistically significant reduction in CIN with statin use (pooled risk ratio, 0.53; 95% CI, 0.37 to 0.76), with a number needed to treat of 45 (95% CI, 30 to 217). Four studies with a total population of 3,647 were included to reach this conclusion; one study included only patients with CKD, two included only patients with cardiac issues, and one included only patients with diabetes. Half of these studies had at least one important limitation (in allocation concealment or blinding of participants and personnel) but were designed to measure CIN as the primary outcome and consistently showed a benefit in reducing CIN in favor of the statin drug, with relatively precise estimates. The number needed to treat was higher for statins than for high-dose N-acetylcysteine despite having a lower pooled risk ratio estimate because of differences between the two groups of studies in the baseline risk of CIN.

The SOE was insufficient that mortality, the need for renal replacement therapy, cardiac events, and hospital length of stay did not differ between statins plus intravenous fluids versus intravenous fluids alone. Most of the studies addressing these outcomes had at least one important study limitation and were consistent but imprecise. One observational study showed results similar to the RCTs. The pooled estimate of the risk ratio for statins plus N-acetylcysteine versus N-acetylcysteine alone was both statistically significant and clinically important (pooled risk ratio, 0.58; 95% CI, 0.39 to 0.86), with a number needed to treat of 41 (95% CI, 14.4 to 60.1). Two studies included only CKD patients, one included patients with cardiac issues, and one had a general population. The CI was wide enough that a clinically unimportant difference cannot be ruled out. The SOE was low and was limited by the imprecision of the studies.

The SOE was insufficient that mortality, the need for renal replacement therapy, cardiac events, and hospital length of stay did not differ between statins plus N-acetylcysteine versus N-acetylcysteine alone. Most of the studies addressing these outcomes had at least one important study limitation and were consistent but imprecise.
Adenosine Antagonists

The SOE was insufficient when studies compared adenosine antagonists plus intravenous saline versus intravenous saline alone because the CI was so wide that we could not rule out either a clinically important decrease or a clinically important increase in CIN (pooled risk ratio, 0.83; 95% CI, 0.08 to 8.17). The SOE was insufficient to make conclusions about the impact of adenosine antagonists on the need for renal replacement therapy, cardiac events, mortality, or length of hospitalization.

Renal Replacement Therapy

The pooled analysis for the three studies of hemodialysis compared with intravenous saline yielded a pooled risk ratio of 1.42, which is consistent with a clinically important increased risk of CIN. The corresponding 95% CI was 0.91 to 2.20, which is consistent with either an increased risk or no important difference. Although the studies on hemodialysis had high risk of bias, the results were consistent enough and precise enough to provide low SOE that hemodialysis does not reduce the risk of CIN when compared with intravenous saline. Two RCTs compared hemofiltration to intravenous saline and reported that patients with severe CKD may have a lower incidence of CIN with hemofiltration, but the SOE was insufficient to support a conclusion. The SOE was insufficient to make conclusions about the impact of using hemodialysis or hemofiltration on mortality, cardiac events, the need for subsequent renal replacement therapy, or the length of hospitalization.

Ascorbic Acid

From studies of the effect of ascorbic acid plus intravenous fluids compared with intravenous fluids alone, the pooled risk ratio was 0.77 (95% CI, 0.56 to 1.05), indicating a small effect that is clinically unimportant and statistically insignificant. The pooled estimate of the effect of ascorbic acid compared with N-acetylcysteine demonstrated a statistically insignificant and not clinically important reduced risk of CIN with ascorbic acid use (pooled risk ratio, 0.92; 95% CI, 0.52 to 1.61). The SOE was low for both comparisons.

Other Comparisons

Although we found many studies investigating other interventions (Table A), the evidence generally was insufficient to support conclusions regarding their comparative effectiveness.

Table A. Miscellaneous comparisons for which evidence was insufficient

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-acetylcysteine</td>
<td>Dialysis, ascorbic acid, nebivolol, atorvastatin, aminophylline, theophylline, fenoldopam, misoprostol</td>
</tr>
<tr>
<td>Intravenous sodium bicarbonate</td>
<td>Acetazolamide, long-term vs. short-term intravenous sodium bicarbonate, intravenous saline in 5% dextrose, oral sodium bicarbonate</td>
</tr>
<tr>
<td>N-acetylcysteine plus intravenous sodium bicarbonate</td>
<td>Intravenous saline and N-acetylcysteine, furosemide plus saline plus N-acetylcysteine, placebo plus sodium bicarbonate, sodium bicarbonate</td>
</tr>
<tr>
<td>Diuretics (furosemide, mannitol, and acetazolamide)</td>
<td>Intravenous saline</td>
</tr>
<tr>
<td>Vasoactive agents (fenoldopam, calcium antagonists, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, beta-blockers)</td>
<td>Intravenous saline</td>
</tr>
<tr>
<td>Antioxidants (probucol, pentoxifylline)</td>
<td>Different hydration regimens</td>
</tr>
<tr>
<td>Fluid administration (various)</td>
<td>Fluid administration (various)</td>
</tr>
<tr>
<td>Dopamine (or dopamine plus furosemide)</td>
<td>Dopamine, furosemide, mannitol, intravenous saline</td>
</tr>
</tbody>
</table>
Discussion

Numerous interventions have been used in studies to reduce the risk of CIN. Remarkably, the strongest evidence of a clinically important benefit was seen in studies of statins used with intravenous saline compared with intravenous saline alone (moderate SOE) and studies of statins plus N-acetylcysteine compared with N-acetylcysteine alone (low SOE). All of the studies included in those meta-analyses were of patients receiving intra-arterial contrast media, so no evidence exists on the potential benefit of statins in patients receiving intravenous contrast media. In the analysis of N-acetylcysteine plus intravenous saline compared with intravenous saline alone, both low-dose and high-dose N-acetylcysteine had only a small, clinically unimportant decrease in the risk of CIN in patients receiving either intra-arterial or intravenous contrast media. The only evidence of a clinically important reduction in CIN was seen when N-acetylcysteine plus intravenous saline was compared with intravenous saline alone in patients receiving LOCM (low SOE). One study has questioned whether N-acetylcysteine is effective at preventing CIN or if it simply reduces serum creatinine.\textsuperscript{10} This is an important finding; however, the reduction in serum creatinine reported as significant was measured at 4 hours, and it was insignificant at 48 hours, which was the timeframe for the measure of CIN in this report. Intravenous sodium bicarbonate did not appear to be any more effective than intravenous saline (low SOE). However, a clinically important reduction in CIN was seen when sodium bicarbonate with IV saline was compared with IV saline in studies using LOCM. Ascorbic acid plus intravenous saline was not more effective than intravenous saline alone (low SOE). For other interventions and comparisons included in this report, the SOE was insufficient to support a definite conclusion because, in general, the studies had important limitations, the comparators varied too much, the effects were inconsistent and imprecise, and the magnitude of effect was weak. Although usual care often involves administration of intravenous fluids, the evidence was insufficient to support a conclusion about the relative effectiveness of intravenous versus oral fluids, or whether fluids should be given before or after the procedure.

Despite the large body of evidence on N-acetylcysteine, the SOE was low, primarily because of limitations in the quality of many of the studies and inconsistency in results across studies, with the possibility of an effect too small to be clinically meaningful. The low SOE helps to explain why N-acetylcysteine is not used more often in clinical practice and why professional organizations offer differing recommendations about the use of N-acetylcysteine to prevent CIN. The joint American College of Cardiology/American Heart Association 2012 guideline recommends against use of N-acetylcysteine for patients receiving intra-arterial contrast in cardiac procedures.\textsuperscript{11} In comparison, the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury suggests using oral N-acetylcysteine with intravenous fluids in patients at increased risk for CIN, while acknowledging that the quality of evidence is very low.\textsuperscript{12} Although N-acetylcysteine is inexpensive and appears to be safe, the evidence may not be strong enough to support a firm policy of routine use, especially in the absence of stronger evidence on clinical outcomes other than the incidence of CIN.

For clinicians who want to reduce the risk of CIN in patients receiving LOCM or IOCM, the best evidence of potential benefit was seen with use of a statin. The SOE on statins versus intravenous saline was moderate, with a CI suggesting at least a 20-percent relative reduction in the risk of CIN. Despite previous systematic reviews highlighting the existence of this evidence on the effectiveness of statins in lowering the risk of CIN, statins are not used routinely in clinical practice to prevent CIN. Furthermore, we are not aware of any professional guidelines recommending their use for this indication. It is possible that the findings reported in the studies of statins could be partly explained by a direct effect of statins on glomerular filtration rate that is independent of a protective effect on kidney function, as has been reported in one study.\textsuperscript{13} However, with increasing recognition of the beneficial cholesterol-independent vascular effects of statins, it may be time to reassess the role of statins in preventing CIN, especially since statins are readily available, easy to administer, and relatively inexpensive.

Our primary analysis showed that intravenous sodium bicarbonate did not produce a clinically important decrease in CIN compared with intravenous saline, contrary to the conclusion of a recent meta-analysis.\textsuperscript{14} This difference in conclusions can be attributed to the fact that the other meta-analysis included five studies that used a combination of intravenous sodium bicarbonate and N-acetylcysteine, which we excluded from our analysis of the effects of sodium bicarbonate. However, in a sensitivity analysis, we found low SOE for a clinically important benefit in decreasing CIN when sodium bicarbonate was compared with intravenous fluids in patients at increased risk for CIN when sodium bicarbonate was used in studies with LOCM. This finding suggests that intravenous sodium bicarbonate could have a role in preventing CIN, but only in patients receiving LOCM.
Future Research

Future studies of the comparative effectiveness of interventions for preventing CIN should stratify patients according to their baseline risk of CIN, especially since it may be difficult to detect a treatment effect in patients having a low risk of CIN. Patients with normal or near-normal serum creatinine may have a lower risk for developing CIN than those with higher serum creatinine levels. Also, patients with risk factors for CKD have a higher risk of developing CIN than patients without such risk factors. Unfortunately, we had a limited ability to stratify the analysis according to baseline risk because almost all studies had a mixed patient population and did not report the results separately by baseline risk.

More research could help to strengthen the evidence about whether N-acetylcysteine or intravenous sodium bicarbonate would be beneficial in a particular clinical context, such as patients with an increased risk of developing CIN who will be receiving LOCM. Given the evidence from our primary analysis showing that intravenous sodium bicarbonate did not produce a clinically important reduction in CIN compared with intravenous saline and did not differ in head-to-head comparisons with N-acetylcysteine, it may be difficult to justify additional RCTs of intravenous sodium bicarbonate unless they focus on particular groups of patients having a higher risk of developing CIN.

The clinically important benefit of statins demonstrated in this analysis provides a rationale for further studies investigating whether the effect differs by statin dose, timing of administration, type of contrast media, or baseline risk of the patient population. Further investigation into the findings on statins versus intravenous saline could be performed through examination of the possible effect of risk modifiers, such as baseline kidney function, concurrent use of nephrotoxic medications, and patient demographics. Future studies could explore the effect of statins on reducing CIN when contrast media are administered intravenously. In addition, studies could be done in individuals without cardiovascular risk factors to determine whether the effectiveness of statin therapy in reducing CIN occurs in the absence of the physiologic effects of statins on coexisting cardiovascular disease.

Little evidence exists on the comparative effectiveness of different regimens for giving fluids to patients receiving contrast media, despite the fact that current clinical practice often involves use of oral hydration alone for studies with intravenous contrast media. If oral hydration were shown to be as effective as intravenous saline, it would be a simple and potentially cost-effective strategy for preventing CIN. Unfortunately, very few studies investigated oral hydration versus intravenous saline. Hence, more studies are needed to investigate the effectiveness of oral hydration versus intravenous saline, especially for intra-arterial contrast procedures such as coronary angiography.

Finally, it is very difficult to apply the existing evidence to patients receiving intravenous contrast media because the vast majority of studies focused on patients receiving intra-arterial contrast media. The risk of CIN may be low enough with the intravenous administration of LOCM and IOCM to make it very difficult to demonstrate the effectiveness of an intervention for preventing CIN. To determine the effectiveness of interventions for preventing CIN in patients receiving intravenous contrast media, it may be necessary to perform large studies of patients having a high risk for developing CKD.

Regardless of which populations or interventions are involved, it is important that future studies use an accepted definition of CIN and report outcomes beyond CIN that are important to patients. Critical for future studies is more standardized reporting on adverse outcomes, such as drug side effects, need for hemodialysis, length of hospitalization, quality of life, and mortality.

To develop more effective interventions for preventing CIN, it may be necessary to conduct additional research on the pathophysiologic mechanisms by which contrast media may contribute to acute kidney injury. It would be important to differentiate the direct effects of contrast media from other factors that can contribute to acute kidney injury in patients receiving intravenous or intra-arterial contrast media.

Conclusions

Of all the interventions that have been used to reduce the risk of CIN, only three have evidence to support a clinically important benefit, and the low-strength evidence of their benefit is limited to specific contexts. Statins with intravenous saline reduce the risk of CIN, whether compared with intravenous saline alone or with N-acetylcysteine, but the evidence is limited to patients receiving intra-arterial contrast media. N-acetylcysteine with intravenous saline, compared with intravenous saline alone, appears to have a small benefit in reducing the risk of CIN, but only in patients receiving LOCM. Similarly, in patients receiving LOCM, sodium bicarbonate appears
to have a small benefit in reducing the risk of CIN when compared with intravenous saline.

References


Full Report