Design of Clinical Trials in Acute Kidney Injury: A Report from an NIDDK Workshop—Prevention Trials

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Summary

AKI is an important clinical problem that has become increasingly more common. Mortality rates associated with AKI remain high despite advances in supportive care. Patients surviving AKI have increased long-term mortality and appear to be at increased risk of developing CKD and progressing to ESRD. No proven effective pharmacologic therapies are currently available for the prevention or treatment of AKI. Advances in addressing this unmet need will require the development of novel therapeutic agents based on precise understanding of key pathophysio-logical events and the implementation of well designed clinical trials. To address this need, the National Institute of Diabetes and Digestive and Kidney Diseases sponsored the "Clinical Trials in Acute Kidney Injury: Current Opportunities and Barriers" workshop in December 2010. The event brought together representatives from academia, industry, the National Institutes of Health, and the US Food and Drug Administration. We report the discussions of workgroups that developed outlines of clinical trials for the prevention of AKI in two patient populations: patients undergoing elective surgery who are at risk for or who develop AKI, and patients who are at risk for contrast-induced AKI. In both of these populations, primary prevention or secondary therapy can be delivered at an optimal time relative to kidney injury. The workgroups detailed primary and secondary endpoints for studies in these groups, and explored the use of adaptive clinical trial designs for trials of novel preventive strategies to improve outcomes of patients with AKI.

Clin J Am Soc Nephrol 7: 851–855, 2012. doi: 10.2215/CJN.12811211

Introduction

The successful prevention and treatment of AKI remains elusive—there are no drugs approved by the US Food and Drug Administration (FDA) to treat AKI. Past clinical studies have been hampered by low statistical power, poorly timed administration of drugs, and adverse medication effects. This unmet clinical need is a high priority and prompted the National Institute of Diabetes and Digestive and Kidney Diseases to sponsor the "Clinical Trials in Acute Kidney Injury: Current Opportunities and Barriers" workshop in December 2010. The event was held at the National Institutes of Health (NIH), and brought together academic investigators, industry partners, and representatives from the NIH and the FDA to address this problem. Two working groups convened and addressed key questions pertaining to the design of clinical trials of interventions for the prevention or treatment of AKI. Discussions focused on two types of clinical settings in which AKI occurs to explore meaningful and specific trial design information. We present suggestions for the design of clinical trials to prevent AKI after elective surgery or radiocontrast administration to improve outcomes of patients with AKI.

Prevention Trial: After Elective Surgery (Cardiopulmonary Bypass, Abdominal Surgery)

Moderators: Dr. Vernon M. Chinchilli and Dr. Kathleen D. Liu

Relatively few interventional trials have been conducted in the postsurgical population, even though this population provides the opportunity to identify and consent patients preoperatively and identify the time of a renal insult, offering investigators the ability to deliver a pharmacotherapy at an optimal time relative to kidney injury. On the other hand, there are challenges in conducting clinical trials in the cardiac surgery population. First, the overall risk of AKI is low (on the order of 1%–10%, depending on the definition of AKI used) and there is uncertainty regarding clinical trial endpoints. Therefore, appropriately sized phase 2 clinical trial designs are needed that enroll a higher-risk patient population (prognostic enrichment) and use clinically important endpoints such as need for dialysis and medium- and long-term changes in kidney function. Second, although including patients at the highest risk of AKI, such as those who have complex operative and perioperative courses or who have baseline CKD, increases the event rate, there is a potential risk that therapeutic

interventions may be less efficacious in these patients. Third, there is a lack of clear understanding of how changes in kidney function should be defined in the context of the cardiac surgery population, necessitating additional dialogue with regulatory agencies such as the FDA.

What Are the Ideal Characteristics of Patients Who Should Be Selected for Postelective Surgery AKI Intervention Trials? The relatively low event rates for AKI in the overall postelective surgery population will require clinical trials to focus on higher-risk patients to increase the event rate and decrease the required sample size. A proposed strategy is to preselect patients at moderate to high risk (incidence of AKI of 15%–20%) for potential inclusion in a clinical trial. Consent could be obtained preoperatively because from a practical standpoint it is much more difficult to obtain timely consent from patients or their surrogates after a procedure. Postoperatively, patients should be randomized on the basis of additional clinical data, including intraoperative course or biomarkers, as was done in a recent clinical trial of erythropoietin for early AKI (1). However, several caveats and gaps in knowledge make implementation of this strategy challenging at present. First, although severity of illness scores such as the Cleveland Clinic or Parsonnet scoring systems (2,3) could be used to preselect patients and enrich a population for patients at higher risk for AKI, it must be recognized that a significant number of patients who develop postoperative AKI are from low-risk preoperative groups. It may be that in these lower-risk individuals, the intraoperative and perioperative courses play a critical role in the development of AKI. Second, there are insufficient data on the use of enrichment and alternative outcome (surrogate) biomarkers in clinical trial design. In both contexts of use, it will be necessary to know which biomarker or panel of biomarkers to use and when and how frequently to measure them. More observational and phase 2 studies are needed to better estimate the event rates and absolute number of events in each group in the selected population. Additional data from "low-risk" populations should be considered, although logistical difficulties may obligate the use of historical controls in some settings. The independent predictive value of perioperative and intraoperative clinical risk factors such as bypass time and hypotension should be compared and contrasted with that of biomarkers because biomarker assays are expensive and time-consuming. It is premature to recommend biomarkers as alternative (intermediate or surrogate endpoint) outcomes for clinical trials of prevention of AKI. There are limitations to this approach, including a lack of generalizability to populations or centers outside the database used, the retrospective nature of the data, and temporal changes in event rates. Possible sources for such databases include data from large academic medical centers or large surgical societies (e.g., the Society of Thoracic Surgeons).

Exclusion criteria for clinical trials should focus on patients who are unlikely to benefit from the intervention. For example, patients with many intraoperative risk factors, who will almost certainly develop AKI, in which the course may be unlikely to be modified by the intervention (e.g., the patient who has cardiogenic shock postoperatively and requires a ventricular assist device for cardiac support) should be excluded. Although CKD is a major risk factor for AKI, patients with advanced CKD, in whom there are few clinical or preclinical data, may not benefit from an intervention to the same extent as individuals with normal or near normal kidney function who possess greater functional reserve. Therefore, it might be appropriate to consider excluding patients with a preoperative estimated GFR (eGFR) of <15 or 20 ml/min per 1.73 m^2 from early clinical trials, recognizing that a limitation of this approach is that interventions that seem to be beneficial may not be generalizable to these high-risk patients.

What Should the Primary and Secondary Study Outcomes Be in AKI Interventional Studies After Elective Surgery? The most appropriate study endpoints will differ in phase 2 compared with phase 3 trials. Reasonable primary endpoints for a phase 2 clinical trial would include progression to Risk, Injury, Failure, Loss of function, and End-stage Renal Disease (RIFLE) stage F or Acute Kidney Injury Network stage 3 AKI (4,5) because a decrease in renal function of this magnitude is associated with high mortality, increased need for renal replacement therapy, prolonged intensive care unit (ICU) stay, and high costs, all of which are important to patients and society. Furthermore, such a decrement in renal function significantly affects how drugs are metabolized and how patients can manage fluid and solute loads. Secondary endpoints might include nonrecovery (defined as progression to RIFLE stage L or ESRD), duration of AKI, ICU and hospital length of stay, disposition or need for rehospitalization, cumulative fluid balance, as well as the need for dialysis. The outcome of "need" for dialysis requires well defined criteria with adjudication because in some cases patients may not be offered dialysis due to a burden of comorbidity and perceived futility, may be offered dialysis and have it refused by patients or family members on other grounds, or may die before dialysis is initiated.

In contrast, phase 3 studies will require more definitive endpoints, such as a composite of death, adjudicated need for dialysis, and lack of functional recovery or progression of kidney disease at 60–90 days. A composite endpoint is necessary because although each component is an important clinical endpoint, the event rate for each individually is likely to be too low to power a phase 3 clinical trial with a feasible sample size. Moreover, a therapeutic agent or strategy that enhances kidney function but results in an increased risk of death would not be desirable. Recent data demonstrate that AKI is associated with poor long-term outcomes (6,7). However, the full effect of nonrecovery or a sustained decline in kidney function (e.g., a 25%, 50%, or 100% rise in serum creatinine concentration [SCr] over a given time interval) has not yet been completely defined. As these data emerge, it will be important to work collaboratively with regulatory agencies, including the FDA, to better understand what definitions of progression of AKI might be considered acceptable for drug approval. Secondary endpoints for phase 3 clinical trials might be similar to those proposed for phase 2 clinical trials, and also include patient-reported outcomes such as functional status or health-related quality of life.

Analogous to other trials in critical care, it would be reasonable to adopt the timing of short-term and long-term event ascertainment after elective surgery at 28 and 90 days, respectively.

How Should Power Analyses and Stopping Guidelines for Studies of Therapies in Postelective Surgery AKI Patients Be Informed? Because the event rate is critical for power analyses for clinical trials and often is based on historical data, in addition to piloting inclusion and exclusion criteria during trial planning, adaptive trial design (8,9) may be a useful strategy for phase 2 and phase 3 AKI clinical trials to reduce the likelihood that these trials are underpowered.

Unlike other settings, there are no guidelines specific to postoperative settings regarding study termination. As always, trials definitively indicating adverse effects should be terminated on safety grounds. With respect to efficacy, clinical trials should be terminated prematurely only when results are unequivocally positive with respect to the prevention or amelioration of clinical events, and not on proposed surrogate or intermediate endpoints, including biomarkers. Efficacy and futility boundaries should take into consideration the risk/benefit ratio of the specific intervention of interest. For example, different futility boundaries would be warranted for extremely safe versus high-risk interventions.

Summary

The working group discussed conducting a prevention trial or early treatment trial of patients undergoing elective surgery (cardiopulmonary bypass or abdominal surgery) who are at risk for or develop AKI. Primary endpoints for phase 2 clinical trials would include progression to RIFLE stage F or Acute Kidney Injury Network stage 3 AKI. Secondary endpoints would include nonrecovery of kidney function, duration of AKI, ICU and hospital length of stay, hospital discharge characteristics or need for rehospitalization, cumulative fluid balance, as well as adjudicated need for dialysis. For phase 3 clinical trials, the use of short-term changes in SCr (or other measures of GFR) or changes in biomarker levels as secondary endpoints may be premature. Adaptive trial design may be a useful strategy for phase 2 and phase 3 clinical trials to reduce the likelihood that studies are underpowered. The group discussed working collaboratively with regulatory agencies, including the FDA, to define parameters of progression and endpoints of AKI that might be considered acceptable for drug approval.

Prevention Trial: Contrast-Induced AKI
**Moderators: Dr. Alfred K. Cheung and
Dr. Steven Weisbord**

Contrast-induced AKI (CI-AKI) is relatively uncommon in the general population. Conversely, CI-AKI occurs in a substantial proportion of high-risk patients and is associated with significant short-term and long-term morbidity and mortality. Angiographic procedures are commonly not performed in patients with CKD, which may be related to providers' concern regarding the development of CI-AKI (10–12). The large and growing number of patients with CKD and the high volume of procedures using contrast make CI-AKI a significant medical problem worthy of further study and therapeutic intervention.

How Should Priorities Be Set for Choosing AKI Prevention Strategies in Radiocontrast Studies? The current standard of care for prevention of CI-AKI includes volume expansion with intravenous isotonic saline or sodium bicarbonate. Past studies comparing sodium chloride and sodium bicarbonate therapy have yielded inconsistent results (13–15). There was disagreement among workgroup participants regarding whether the effectiveness of sodium bicarbonate was worthy of further study. If a clinical trial studying bicarbonate is conducted, urine pH should be specifically assessed to monitor the physiologic effects of the intervention. There is no convincing evidence that N-acetylcysteine is effective in preventing CI-AKI, but it is still often used because of its low costs and minimal risks.

Studies of preventive interventions such as aminophylline, fenoldopam, atrial natriuretic peptide, prostaglandins, and statins may not prove worthwhile because the efficacy of these agents may be limited, and use of several of these agents has been associated with safety concerns. Conversely, study of novel preventive agents remains important.

What Are the Characteristics of Patients Who Should Be Selected for Radiocontrast AKI Prevention Trials? To yield adequate event rates to make clinical trials practical, the target population should be at high risk for CI-AKI. Suggested inclusion criteria are an eGFR of 15–44 ml/min per 1.73 m^2 or an eGFR of 45–60 ml/min per 1.73 m^2 in the presence of at least one other risk factor such as diabetes, proteinuria, or heart failure. Including patients solely on the basis of the presence of diabetes with normal or near normal kidney function and no proteinuria in studies to prevent CI-AKI would yield a trial population at low risk.

AKI in the setting of a variety of procedures (*e.g.,* cardiac and noncardiac percutaneous interventions, radial or femoral approaches, and angiography without angioplasty) is worthy of further study. Although the volume of contrast has been shown in some studies to be a risk factor for CI-AKI, the utility of using contrast volume as an inclusion criterion is unknown. In general, lower volumes of contrast are associated with a lower incidence of CI-AKI (16). Nonetheless, because of its complexity and unpredictability, the expected volume of contrast should not be an inclusion criterion. The use of iso-osmolal or low-osmolal contrast should be included, whereas high-osmolal contrast should be excluded (17). Most agents to be tested should be administered as primary interventions (*i.e.,* before contrast administration). Secondary prevention studies might have less utility in the setting of CI-AKI than in some other settings, in which the actual timing and duration of the insult are less well demarcated. Longer-term administration of prevention agents beyond 1–2 days might enhance efficacy; however, the effect on study cost needs to be considered, particularly because the majority of persons receiving radiocontrast—even those at high risk for CI-AKI—are managed by "observation" or as outpatients.

What Are the Expected Rates of Nephrotoxicity and Severe Nephrotoxicity in Patients Receiving Radiocontrast? What Are the Data Sources for Contemporary Information on These Rates for Planning Purposes? Data from placebo arms of past clinical trials of CI-AKI suggest that the incidence of a ≥ 0.5 mg/dl and/or $\geq 25\%$ rise in SCr is approximately 10%–15% in patients with a GFR of 15–60 ml/min per 1.73 m^2 (2,11,14,18,19). The incidence of AKI requiring dialysis is likely to be approximately 1%–1.5%. Event rates from clinical trials are quite variable, in part due to diverse inclusion criteria and discrepant definitions

of primary and secondary outcomes. Other possible sources of event rate data include databases from the Society of Thoracic Surgeons and from integrated healthcare systems such as health maintenance organizations or the Veterans Administration. The use of retrospective data to define projected event rates, however, could be subject to bias.

What Should the Primary and Secondary Study Outcomes Be in Radiocontrast AKI Prevention Trials, and What Are the Most Appropriate Data Sources to Inform Planning? For phase 2 studies, the primary outcome should be defined by an increase in SCr of ≥0.5 mg/dl and/or ≥25%, with serial measurements of SCr over a minimum of 96 hours. Currently, the FDA will not accept a short-term rise in SCr as a sufficient primary endpoint for a phase 3 registration trial. Patient-centered clinical outcomes such as death, adjudicated need for acute dialysis, myocardial infarction, stroke, and all-cause non-elective hospitalization have been proposed and are being used in ongoing trials. Designs using patient-centered outcomes will require a larger number of trial participants.

Sustained loss of kidney function, as measured by an increase in SCr or other measures of GFR over a period of time (*e.g.*, 90 days), represents more than merely a biomarker parameter, and is an acceptable endpoint for a phase 3 trial; however, the event rate will be relatively low. Use of a composite endpoint including other clinical events is, therefore, probably necessary. There is a need for further discussion with the FDA to clarify the importance of and qualification pathway for short-term changes in renal function and other alternative (surrogate) outcomes in specific contexts of use (prevention of CI-AKI or prevention of postsurgery AKI). For example, future studies might examine if preventing a short-term increase in SCr results in lower rates of patient-centered events in order to qualify the use of short-term changes in SCr or other measures of GFR as alternative (surrogate) outcomes for phase 3 studies.

What Are the Data Regarding Potential Biomarkers and Surrogate Outcomes to Be Used in Studies of AKI Prevention Strategies in Patients Receiving Radiocontrast? There are currently insufficient data to permit the use of serum or urine biomarkers as inclusion criteria, or prognostic enrichment or risk stratification variables for CI-AKI studies. Some biomarkers may be appropriate outcomes for phase 2 trials if they are measured along with SCr. However, ancillary studies focused on the collection of biomarkers should be considered whenever possible in clinical studies, especially in randomized clinical trials, so that their utility in AKI can be ascertained. These data would facilitate the planning of future studies.

What Are the Risk/Benefit Considerations That Should Be Taken into Account in Considering Patients Receiving Radiocontrast? How Will Assessments Differ in Pilot/Feasibility Versus Definitive Outcome Studies for AKI Prevention? An important issue to consider in weighing the risk/benefit ratio of an intervention to prevent CI-AKI is the benefit that patients may derive from undergoing procedures that require contrast (*e.g.*, cardiac catheterization) and the risk of not undergoing such a procedure (*e.g.*, myocardial infarction or cardiac death). Although it is difficult to quantify the risks of CI-AKI prevention strategies without specification, a modest risk for a preventive intervention might be acceptable for a high-risk subpopulation, given

the significant morbidity and mortality associated with CI-AKI. Risk/benefit considerations may have an effect on the selection of endpoints. For preventive strategies that are exceedingly safe, an alternative outcome biomarker that has been shown to predict patient-centered outcomes might be qualified to be considered as a major endpoint. For higher-risk strategies, hard clinical endpoints are likely to be necessary.

How Should Power Analyses for Studies of Therapies in Radiocontrast AKI Patients Be Informed? How Should Stopping Guidelines Be Used in Radiocontrast AKI Studies? Sample size requirements of studies using interventions that have already been tested (*e.g.*, N-acetylcysteine), or with similar effect sizes, will be very large if hard "patient-centered" outcomes are used, given their modest effect sizes.

At present, trials should not be terminated prematurely on the basis of results of biomarkers as outcome measures. Clinical outcome data should continue to be collected.

Summary

The generalizability of the results of future trials of CI-AKI is an important consideration. Intravascular volume expansion is currently the only effective prevention strategy for CI-AKI, but there is a need for standardized volume expansion procedures. Future trials should, at least in part, focus on novel preventive strategies. Practical inclusion criteria for a prevention trial would be CKD based on a GFR of 15–59 ml/min per 1.73 m² and the presence of at least one other risk factor such as heart failure, diabetes, or proteinuria among patients with an eGFR of 45–59 ml/min per 1.73 m². Event rates for AKI and AKI requiring dialysis are expected to be 10%–15% and 1.0%, respectively, in patients with CKD (20). For phase 2 studies, an appropriate primary study outcome might be an increase in SCr of ≥0.5 mg/dl or ≥25% with multiple SCr assessments over a minimum of 96 hours. Phase 3 studies will require clinical outcomes such as adjudicated need for dialysis, death, rehospitalization for renal causes, or long-term change in GFR. However, increases in SCr of shorter durations, such as 96 hours to 90 days, may have significant effects on long-term clinical outcomes but need to be qualified to be used as an alternative to a hard clinical outcome.

Disclosures
None.

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