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COMMENTARY

Lessons learned from the PRESERVE trial

[1,2]SASAN PARTOVI, MD, [3]THOMAS TRISCHMAN, BS and [2]PREET S KANG, MD

[1]Section of Vascular and Interventional Radiology, Department of Radiology, University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, OH, USA
[2]Section of Interventional Radiology, Department of Radiology, Louis Stokes Cleveland Veterans Affairs Medical Center, Cleveland, OH, USA
[3]School of Medicine, Case Western Reserve University, Cleveland, OH, USA

Address correspondence to: Dr Sasan Partovi
E-mail: *sxp509@case.edu*

ABSTRACT

The recently published Prevention of Serious Adverse Events Following Angiography (PRESERVE) trial is presently the largest and most comprehensive clinical trial comparing commonly applied strategies for prevention of iodinated contrast-induced acute kidney injury in high-risk patients. The fundamental conclusion of the PRESERVE trial is that oral acetylcysteine and i.v. sodium bicarbonate are not superior to simple i.v. hydration with isotonic saline for the prevention of contrast-induced renal sequelae. In this commentary, we discuss the results in the context of selected past major trials, and provide insights into the strengths and potential weaknesses of the PRESERVE trial. In the future, developing individualized preventive approaches to avoid contrast-induced acute kidney injury for different patient populations is recommended.

INTRODUCTION

Currently suggested strategies aimed at preventing iodinated contrast-induced acute kidney injury and associated long-term renal complications include administration of i.v. saline, i.v. sodium bicarbonate and oral acetylcysteine. Due to the minimal associated side effects and relatively low costs, i.v. sodium bicarbonate and oral acetylcysteine are widely employed in clinical practice. Yet, until the recent Prevention of Serious Adverse Events Following Angiography (PRESERVE) trial conducted by Weisbord et al, there was limited evidence to demonstrate the efficacy of these treatments at preventing long-term kidney injury.[1]

MECHANISMS OF NEPHROPROTECTIVE MEDICATION STRATEGIES

The potentially nephroprotective mechanisms of both acetylcysteine and sodium bicarbonate are poorly understood, as are the actual underlying mechanisms of nephrotoxicity of iodinated contrast agents. Some have even cast doubt on the claim that contrast media is a cause of acute kidney injury.[2] However, *in vivo* models have demonstrated that following iodinated contrast injection, there is a subsequent decline in medullary blood flow and a simultaneous increase in tubular transport activity, thereby resulting in hypoxia and generation of reactive oxygen species (ROS).[3-5] These ROS presumably act as the mediators of renal tubule cell damage, leading to necrotic or apoptotic events.[6]

It was previously speculated that sodium bicarbonate could be nephroprotective against iodinated contrast-induced toxicity by increasing the pH within the renal tubules, which may attenuate the chemical reaction generating hydroxyl radicals from hydrogen peroxide; hence the amount of ROS produced is decreased and less tubular damage occurs.[7] Acetylcysteine is thought to function by increasing production of glutathione, which acts as an antioxidant that could potentially buffer against the nephrotoxic effects of the increased ROS generated post-iodinated contrast administration.[8]

SUMMARY OF THE PRESERVE TRIAL

The PRESERVE trial was a randomized, double-blinded, placebo-controlled trial with over 5000 enrolled patients, who were deemed to be at high risk of developing iodinated contrast-induced acute kidney injury. It included non-diabetic patients with an estimated glomerular filtration rate between 15 and 44.9 ml per minute per 1.73 m^2 of body-surface area and diabetic patients with an estimated glomerular filtration rate between 45 and 59.9 ml per minute per 1.73 m^2 of body-surface area. The trial excluded patients undergoing emergency angiography and patients with unstable levels of serum creatinine. It employed a two-by-two factorial design to assign patients scheduled to undergo angiography to receive either i.v. 1.26% sodium bicarbonate or i.v. 0.9% sodium chloride, and either 5 days

of oral acetylcysteine or placebo, with approximately 2500 patients assigned to each group. Patients receiving i.v. sodium bicarbonate or i.v. sodium chloride were administered a total volume of 3 to 12 ml per kg before angiography, and 6 to 12 ml per kg after angiography. 1200 mg doses of oral acetylcysteine were given an hour before angiography, an hour after angiography and continued twice daily for the following 4 days. Patients were administered iodinated intra-arterial contrast agent during angiography, resulting in a median volume of 85 ml of contrast medium administered per patient. All patients received either iso-osmolal contrast media or non-ionic, low-osmolal contrast media. Selection of specific contrast media was determined by the discretion of the treating physician at each site. The study design was strong, with enrollment of a significant number of patients, clear definition of end points and analysis of outcome data at approximately 90 to 100 days post-angiography. This sets the PRESERVE trial apart from existing studies on prevention techniques for iodinated contrast-induced acute kidney injury. The primary end point of the PRESERVE trial was defined as a composite of death, dialysis requirement, or a persistent serum creatinine increase of at least 50% from baseline at approximately 90 to 100 days post-angiography. The secondary end point was defined as the occurrence of acute kidney injury; namely, an increase in serum creatinine of either at least 25% or 0.5 mg per deciliter from baseline in the first 3 to 5 days following angiography. The primary end point of the PRESERVE trial examining intermediate- to long-term (90–100 days post-angiography) consequences of contrast-induced acute kidney injury could be more clinically relevant than the short-term and transient increase in serum creatinine that prior studies have used to define contrast-induced acute kidney injury. [9,10]

Based on these end points, the PRESERVE trial found at a pre-scheduled interim analysis that the primary end point occurred in 4.4% of patients receiving i.v. sodium bicarbonate, and 4.7% of patients receiving i.v. hydration with sodium chloride, which was not significantly different. Similarly, the primary end point occurred in 4.6% of patients receiving 1200 mg oral acetylcysteine, and 4.5% of patients receiving oral placebo, respectively, which was again not significantly different. Results for the secondary end point had similar findings, with 9.5% of sodium bicarbonate group patients and 8.3% of sodium chloride group patients experiencing contrast-associated acute kidney injury. This difference between the two groups was also not statistically significant. The same was true for the occurrence of contrast-associated acute kidney injury when comparing the oral acetylcysteine group to the oral placebo group, with rates of 9.1 and 8.7%, respectively (not statistically significant). Based on the lack of significant findings between treatment and placebo groups at the time of the aforementioned interim analysis, the PRESERVE trial was terminated prior to the planned enrollment of 7680 patients as determined by pre-trial statistical power analysis.

Selected major trials before PRESERVE

Prior studies have attempted to evaluate the relative effectiveness of acetylcysteine and i.v. sodium bicarbonate compared to i.v. hydration with sodium chloride, but these studies had fewer patients and focused more on acute kidney injury as opposed to intermediate-term renal sequelae of contrast-induced acute kidney injury.

Merten and colleagues compared administration of i.v. sodium bicarbonate with standard i.v. sodium chloride hydration.[11] They found that there was a significant difference in occurrence of acute iodinated contrast-induced acute kidney injury between the groups, with a rate of 1.7% in the sodium bicarbonate group *vs* 13.6% in the sodium chloride group. Compared to the PRESERVE trial this study was much smaller scale. There were not only fewer patients to assess but also very few events to analyze. While the PRESERVE trial was a multinational, multicenter study with roughly 5000 patients, Merten et al was a single center study with a total of 119 patients. These patients were further divided into the two groups, and the end point event occurred in 8 of 59 sodium chloride group patients, and only 1 of 60 sodium bicarbonate group patients. It needs to be considered that in contrast to the PRESERVE trial, this study enrolled a more heterogeneous group of patients receiving iodinated contrast; the PRESERVE trial only included patients undergoing angiography, while Merten et al included patients undergoing both CT and angiography. Finally, the end point of the study from Merten et al lines up with the secondary end point of the PRESERVE trial and was essentially related to acute contrast-induced acute kidney injury. However, Merten et al did not have an end point similar to the composite primary end point of the PRESERVE trial, which focused on intermediate-term renal sequelae of iodinated contrast.

The RENO study was another relevant trial, which attempted to assess the effects of oral acetylcysteine combined with i.v. sodium bicarbonate in angiography patients.[12] This trial was a single-center, prospective randomized controlled trial with 111 acute coronary syndrome patients who underwent emergency percutaneous coronary intervention. The treatment group received i.v. sodium bicarbonate with 2400 mg of acetylcysteine an hour before contrast injection, followed by 12 h of i.v. sodium chloride following the procedure. The treatment group received two 600 mg doses of oral acetylcysteine the day after the procedure. The control group received the same 12 h of i.v. saline following the procedure and the two doses of oral acetylcysteine the following day, but did not receive sodium bicarbonate or acetylcysteine before the procedure. The RENO trial found a significant difference between the two groups with regard to contrast-induced acute kidney injury, defined as an absolute increase in serum creatinine of 0.5 mg per deciliter from baseline in the three days post-emergency coronary intervention. The treatment group had a contrast-induced acute kidney injury rate of 1.8% (1/56), while the control group showed a rate of 21.8% (12/56). These results seem to contradict the findings of the PRESERVE trial. However, there are several important considerations. First, the PRESERVE trial excluded patients undergoing emergency angiography, so the difference may be related to the analyzed patient group. Second, the pre-procedure acetylcysteine was administered via i.v. route in the RENO trial, while it was administered orally in the PRESERVE trial. This difference could confound efforts to compare drug effects due to the elimination of first pass

metabolism with i.v. administration. Third, the dose of acetylcysteine was higher in the RENO trial than it was in the PRESERVE trial (2400 mg *vs* 1200 mg). The most important limitation of the RENO trial is the low number of detected events, which is a problem the PRESERVE trial overcame. Finally, this study again focused once again on acute contrast-induced acute kidney injury whereas the composite primary end-point of the PRESERVE trial assessed renal complications 90 to 100 days post-angiography. Therefore, the composite primary end-point of the PRESERVE trial may be more clinically relevant, whereas there is a possibility that the acute contrast-induced acute kidney injury as assessed in the RENO trial may resolve over time.

Another major trial in this field was performed by the Acetylcysteine for Contrast-induced nephropathy Trial (ACT) Investigators.[13] The ACT study compared the effects of oral acetylcysteine to placebo for preventing acute iodinated contrast-induced acute kidney injury. This study was very similar to the PRESERVE trial in several ways. First, the ACT study only included patients undergoing angiography. Second, it was a large, multicenter, randomized controlled trial involving a significant number of patients (n = 2308). Additionally, both studies used the same dose of acetylcysteine (1200 mg) in their treatment groups. Interestingly, the findings of the PRESERVE trial were similar to the findings in the ACT study. The trial essentially found that there was no significant difference in the occurrence of iodinated contrast-induced acute kidney injury acutely or after 30 days in the group receiving oral acetylcysteine *vs* the group receiving oral placebo. In both the acetylcysteine group and the placebo group, acute contrast-induced acute kidney injury occurred in 12.7% of patients. Contrast-induced acute kidney injury was defined as a 25% increase in serum creatinine from baseline between 48 and 96 h after angiography. Likewise, death or the need for dialysis at 30 days occurred in 2.2% of acetylcysteine group patients, and 2.3% of placebo group patients, respectively. This difference was statistically not significant.

LESSONS LEARNED FROM PRESERVE

In an editorial dealing with the ACT trial, McCullough et al emphasized the need for a large-scale trial to resolve the inconsistencies in strategies for preventing iodinated contrast-induced acute kidney injury. Such a trial should be aimed at drawing conclusions which would impact clinical practice and patient management.[14] The PRESERVE trial accomplished that, and revealed that hydration with i.v. saline should be the mainstay strategy to prevent iodinated contrast-induced acute kidney injury.

Though well conducted, the PRESERVE trial has several shortcomings worth discussing. The trial excluded patients with unstable baseline levels of serum creatinine. It is understandable that an unstable baseline serum creatinine level would make it more challenging to determine whether or not contrast-induced acute kidney injury had occurred. However, an unstable serum creatinine may relate to acute kidney injury, and patients with acute kidney disease are among those with the highest risk of developing contrast-induced acute kidney injury. Essentially, this excluded population is of high interest because these patients may benefit markedly from strategies to prevent contrast-induced acute kidney injury with associated renal sequelae.

Patients with decompensated heart failure were excluded as well. Administering i.v. fluids to patients in this population undergoing angiography may exacerbate the symptomatology. Therefore, alternative strategies to prevent contrast-induced acute kidney injury in this population may be of useful; specifically, it would be valuable to determine if oral acetylcysteine can help prevent contrast-induced nephrotoxicity in these patients. Another self-acknowledged limitation concerning the patient population of the PRESERVE trial is that males constituted 93.6% of the study sample, which could possibly limit the ability to generalize any conclusions from the trial to female patients.

One additional major limitation of the PRESERVE trial is the relatively low median contrast volume administered, which was 85 ml, which is partially explained by the relatively low number of patients undergoing interventional procedures (approximately 30%). More than two thirds of patients had diagnostic angiography studies. This somewhat limits the ability to generalize the findings of the PRESERVE trial to complex interventional therapeutic procedures, which often require higher administered volumes of iodinated contrast material.

In summary, the PRESERVE trial employed a robust study design, and is both timely and relevant to the daily clinical practice of interventionalists. Although oral acetylcysteine and i.v. sodium bicarbonate are currently widely used for prevention of iodinated contrast-induced acute kidney injury, this trial provides evidence that simple i.v. hydration with sodium chloride is a sufficient strategy to prevent renal sequelae of contrast-induced acute kidney injury. Further investigations or subanalysis are needed to explore which nephroprotective strategies are particularly beneficial in patients undergoing interventional procedures outside the coronary circulation. Patients who may not be able to tolerate i.v. hydration, such as those with congestive heart failure, will likely not benefit from simple i.v. hydration, and in this population nephroprotective therapies need to be explored. In the future, an individualized approach for patients undergoing endovascular interventions is warranted.

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