12-16-2022

Prophylactic intravenous prehydration with sodium bicarbonate or sodium chloride in the prevention of contrast induced acute kidney injury

Briana Lockett
James Madison University

Caroline Dong
James Madison University

Prophylactic Intravenous Prehydration with Sodium Bicarbonate or Sodium Chloride in the Prevention of Contrast Induced Acute Kidney Injury

Caroline Dong, PA-S and Briana Lockett, PA-S

James Madison University

Physician Assistant Program

May 4, 2022

Abstract

Introduction: Iodinated contrast media is a crucial component in the diagnostic work up of many life-threatening illnesses. However, it has been reported to cause acute kidney injury after administration, especially in patients with pre-existing renal disease. Several prophylactic treatments have been studied in hopes of minimizing these adverse events. The current standard of care in this patient population is prophylactic intravenous volume administration with either sodium chloride or sodium bicarbonate. **Objective:** The goal of this literature review is to determine if prophylactic intravenous volume administration with either saline or sodium bicarbonate prior to contrast administration decreases the incidence of contrast induced acute kidney injury (CIAKI). **Methods:** A search of PubMed was performed using terms "kidney diseases/chemically induced" and "contrast media/adverse effects". The limits applied included randomized control trials, published within the last 6 years, human subjects, and adult participants over age 18. **Results:** All three studies demonstrated that there was no statistically significant difference between prehydration and no prehydration in reducing the incidence of kidney injury. **Conclusions:** We recommend further studies be conducted with more standardized patient populations and a precise consensus of desired endpoint. While there are still several unanswered questions regarding the specific outcomes of renal injury after contrast use, the risk of CIAKI in patients with decreased kidney function does not appear to be any higher when prehydration is not used.

Introduction

Iodinated contrast media is widely used as a way to enhance radiologic imaging such as CT scans.[1] Contrast is typically used to differentiate between organ structures and highlight vascular abnormalities that would otherwise go undetected without it.[2] Contrast enhanced CT is used to detect conditions such as pulmonary embolism, aortic dissection, and acute appendicitis.[2] Given its increased accuracy, it has a crucial role in the work up of potentially life-threatening conditions.

Despite its perceived diagnostic benefit, iodinated contrast media has been known to cause acute kidney injury, especially in those with pre-existing renal impairment.[3] This transient phenomenon is known as contrast-induced nephropathy (CIN) or contrast-induced acute kidney injury (CIAKI) and is diagnosed by a decrease in renal function two to five days after intravascular iodinated contrast use.[3] However, this process is typically self-limiting and kidney function generally returns to baseline without any residual long-term consequences in most populations.[1,3] Despite this, various prophylactic treatments have been studied in hopes of minimizing contrast induced acute kidney injury, particularly in those with reduced kidney function.[3] The current standard of care in this patient population is prophylactic intravenous volume administration; however, there is insufficient evidence to prove its efficacy.[1] This treatment strategy leads to increased cost, added logistical difficulties, and potential adverse reactions of its own.[1]

Currently, the two mainstays of intravenous fluid administration are sodium bicarbonate and saline. Isotonic saline has been used to expand intravascular volume prior to contrast, promoting diuresis and dilution of contrast load.[4] Sodium bicarbonate on the other hand, is theorized to neutralize the acidity of the urine and renal medulla, inhibiting the formation of damaging free radicals caused by contrast media.[5] Conflicting studies have been published on the efficacy of one over the other and their usefulness against placebo, with some studies showing sodium bicarb as superior to saline and others showing no added benefit to prophylaxis.[4]

Clinical Question

The goal of this literature review is to determine if prophylactic intravenous volume administration with either saline or sodium bicarbonate prior to contrast administration decreases the incidence of contrast induced acute kidney injury in adults with pre-existing renal disease.

Methods

An initial search of PubMed was performed in October 2021 using the MESH terms “kidney diseases/chemically induced” and “contrast media/adverse effects”. This yielded a total of 3023 non-duplicated articles. Inclusion criteria included randomized control trials published within the last 6 years. Those that were excluded did not use hydration prophylaxis, human subjects, or adult participants over age 18. This left three studies to be included in the quantitative synthesis. Figure 1 shows a PRISMA flow diagram of our systematic review processes.

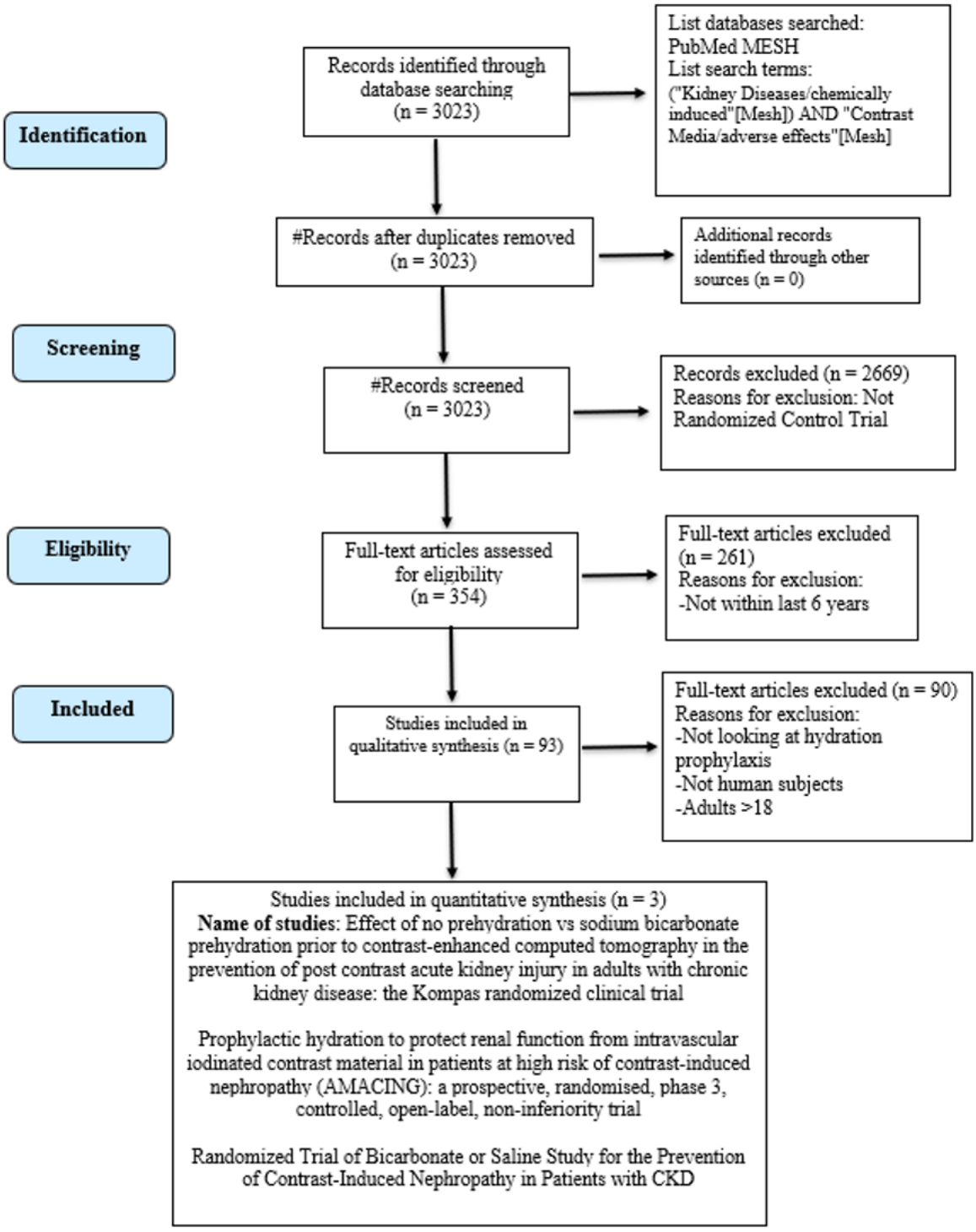

Figure 1: PRISMA flow diagram

Results

Study 1. *Effect of no prehydration vs sodium bicarbonate prehydration prior to contrast-enhanced computed tomography in the prevention of post contrast acute kidney injury in adults with chronic kidney disease: the Kompas randomized clinical trial. Timal et al.*

Study Objective

"To assess the renal safety of omitting prophylactic prehydration prior to iodine-contrast based media administration in patients with stage 3 CKD."[1]

Study Design

The Kompas trial was a multicenter, noninferiority, randomized clinical trial conducted at 6 hospitals in the Netherlands between April 2013 through September 2016. Patients included in this study had stage 3 CKD based on eGFR of 30 to 59 mL/min/1.73 m2 in the presence of diabetes or at least 2 of the following additional comorbidities: peripheral artery disease, congestive heart failure, age older than 75 years, anemia, contrast volume greater than 150 mL, or use of nephrotoxic medication.

A total of 523 patients were randomized in a 1:1 ratio to receive no prehydration or prehydration with 250mL of 1.4% sodium bicarbonate administered in a 1-hour infusion before undergoing elective contrast-enhanced computed tomography. The primary endpoint was the mean relative increase in serum creatinine level compared to baseline 2-5 days after contrast administration with a noninferiority margin of <10% increase. Secondary outcomes were incidence of post contrast acute kidney injury 2-5 days after contrast administration, mean relative increase in creatinine level 7-14 days post contrast, incidences of acute heart failure and renal failure requiring dialysis, and health care costs.

Study Results

The mean relative increase in creatinine level 2-5 days after contrast administration was 3.0% in the no prehydration group vs 3.5% in the prehydration group. Post contrast acute kidney injury occured in 7 of the no prehydration group and 4 of the prehydration group, resulting in a relative risk of 1.7. None of the patients required dialysis or developed acute heart failure. Mean hydration costs were $143.94 per patient in the prehydration group compared to $0 in the no prehydration group. The study concluded that withholding prehydration did not compromise patient safety and is a safe and cost-efficient measure.

Study Critique

Strengths - This study had a noninferiority margin that is clinically relevant (<10%), used intention to treat analysis, and randomization took into consideration comorbidities, age, sex, smoking, renal function, medication use.

Weakness - Contrast media used was not standardized among the different hospitals and depended on hospital preference. Depending on the type of contrast enhanced CT (CECT), different volumes of contrast were administered and long-term adverse effects were not recorded.

Study 2. *Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. Nijssen et al.*

Study Objective

To assess the clinical-effectiveness and cost-effectiveness of prophylactic hydration using 0.95% NaCl in preventing contrast-induced nephropathy in patients with reduced renal function. [3]

Study Design

This was a prospective, randomized, phase 3, parallel-group, open-labeled, non-inferiority study conducted at a university medical center in the Netherlands. Patients included in the study were those 18 years of age or older undergoing an elective procedure requiring iodinated contrast and categorized as high-risk based on eGFR of 45-59 mL per min/1.73m2 with either diabetes or at least two comorbidities (age >75, anemia, cardiovascular disease, or nephrotoxic medication use) or eGFR of 30 to 45 mL per min/1.73m2.

The participants were randomly assigned in 1:1 ratio to receive intravenous 0.9% NaCl or no prophylaxis. Exclusion criteria included patients with eGFR less than 30 mL per min/1.73m2, prior dialysis, or no referral for intravenous hydration. Randomization was done using computer generated screening and enrolment application software. The laboratory workers were blinded to patient treatment. The study analyzed the data based on intention-to-treat and per-protocol. Results between the two did not differ because all randomly assigned patients received their allocated treatment.

The outcome of this study was defined as a rise in serum creatinine from baseline of greater than 25% or 44umol/L within 2-6 days of contrast administration. The study also evaluated the cost-effectiveness of no prophylaxis compared with intravenous hydration in the prevention of contrast-induced nephropathy.

Study Results

A total of 660 patients were included in the study; 332 were randomly assigned to the no prophylaxis group and 328 to the 0.9% NaCl hydration group. Of the hydration group, 32 were excluded because no serum creatinine was available 2-6 days post-contrast and 68 more were excluded after the primary analysis due to no serum creatinine level available on days 26-35 post-contrast. In the group that did not receive intravenous hydration, 25 were excluded because no serum creatinine was available 2-6 days post-contrast and 72 more were excluded after the primary analysis due to no serum creatinine level available on days 26-35 post-contrast. A total of 260 participants in each group were included in the secondary 26-35 day analysis.

Contrast-induced nephropathy occurred in 8 of the 307 participants in the no prophylaxis group and 8 of the 296 participants in the prehydration group. To evaluate the primary endpoint, the researchers calculated the percentage of patients with contrast-induced nephropathy in the non-hydrated group minus those in the hydrated group with a one-sided 95% confidence interval. The absolute difference in the two groups was -0.10% (one-sided 95% CI -2.25 to 2.06;

one-tailed p=0.4710). At 26-35 days post-contrast, serum creatinine values and eGFR were used to compare the incidence of adverse renal events between the standard prophylactic treatment and the no prophylactic treatment groups and no statistically significant differences were found.

Study Critique

Doctors, nurses, and participants were unable to be blinded due to the clear difference in treatment options. All contrast enhanced procedures were done using minimum volume pre-warmed, low-osmolar, monomer, non-ionic, contrast material which might have influenced the incidence of contrast-induced nephropathy. The study also did not use the most commonly accepted definition of contrast-induced nephropathy because they allowed for a longer time frame than the usual 48-72 hours. However, they stated this is because the 2-6 days timeframe they used is more practical in an outpatient setting.

Study 3. *Randomized Trial of Bicarbonate or Saline Study for the Prevention of Contrast-Induced Nephropathy in Patients with CKD. Solomon et al.*

Study Objective

"To assess the effect of high-dose bicarbonate on the clinically significant composite of death, need for dialysis, or sustained reduction in eGFR >20% from baseline at 6 months after the exposure to contrast media"[5]

Study Design

This is a prospective, double-blinded, multicenter randomized clinical trial involving 17 centers across the US with patients 18 years or older that were scheduled for elective coronary or peripheral angiography and had an eGFR <45ml/min per 1.73m^2. Three hundred ninety one patients total were randomized with 193 receiving 1.3% sodium bicarbonate (154 mEq/L) and 196 receiving 0.9% sodium chloride (154 mEq/L). 5 ml/kg was infused 1-hour prior to angiography, and 1.5ml/kg per h during and 4 hrs post angiography. Electrolytes and serum creatinine were obtained within 12 hours before contrast, 1, 3, 7, 30, 90, 180 days after contrast. Primary endpoints were first occurrence of death, renal replacement therapy (RRT), or reduction in eGFR >= 20% confirmed in 2 separate measurements between day 30 and 180. Secondary endpoints were length of hospital stay, mortality and time to death or RRT, acute changes in serum creatinine.

Study Results

The incidence of primary outcome was 14.9% in the bicarbonate group and 16.3% in the control group. There was also no difference in the incidence of CIAKI between treatment groups (14.5% vs 12.1%) and CIAKI was associated with a higher incidence of sustained loss of kidney function at 6 months compared with those without CIAKI (21.2% vs 7.7%).

Study Critique

There was a statistically significant difference in baseline eGFR between the bicarbonate group and the saline group that might have made the results of the analysis favor the saline group. Furthermore, the study ended early and there were not enough participants to reach a statistically

significant difference due to a low power. Lastly, the levels of serum bicarbonate seemed to indicate that this can not be definitely concluded.

Table 1. Overview of Studies

	Timal et al	Nijssen el at	Solomon et al
Patients, N	523	660	391
Gender	M - 336 (64.2%) F - 187 (35.8%)	M - 407 (61.7%) F - 253 (38.3%)	M - 225 (57.5%) F - 166 (42.5%)
Population	Male + Females >18 undergoing non-emergent CECT with CKD stage 3A and 3B in the presence of diabetes or at least 2 risk factors	Male + Females ≥ 18yo undergoing elective procedure requiring contrast with eGFR = 30-59	Male + Females ≥ 18yo undergoing elective coronary or peripheral angiography with eGFR < 45
Primary Outcome	% increase in baseline serum creatinine 2-5 days after contrast admin (noninferiority margin of <10%)	% increase in serum creatinine from baseline of >25% or 44umol/L within 2-6 days of contrast exposure	Death, RRT, reduction in eGFR of ≥20% between day 30-180
Blinding	No	No	Yes
Prehydration	250mL of 1.4% sodium bicarb IV in 1-hr fusion prior to CECT	0.9% NaCl 3-4mL/kg/h IV/IA 4h before and after contrast admin (or 12h depending on protocol)	1.3% sodium bicarb (154mEq/L) 0.9% NaCl (154mEq/L
Results	3% ↑ no prehydration 3.5% ↑ sodium bicarb	2.6% ↑ no prehydration 2.7% ↑ saline	14.9% bicarb 16.3% saline

Discussion

Contrast has long been known to cause kidney injury, especially in those with existing renal impairment.[3] Due to the necessity of contrast in imaging, studies have been done to look into ways to curb potential renal injury following contrast administration, but none show a general consensus on if prophylactic treatment, specifically prehydration, prevents contrast-induced renal injury. The purpose of this review is to determine if prophylactic treatment with either normal saline or sodium bicarb reduces the incidence of CIAKI.

Overview of the three studies is shown in Table 1. Timal et al[1] and Nijssen et al[3] had the most similar study population, with all adults undergoing an elective procedure with an eGFR between 30-59 (CKD stage 3). Both stratified study populations based on risk factors such as diabetes,

age, cardiac disease which was representative of the general population in whom there would be the most concern for adverse renal outcomes. Primary outcomes were also similar, using an increase of serum creatinine several days after the procedure, but the percentage increase of what they considered to be indicative of AKI were different, with Nijssen et al[3] requiring a higher threshold than Timal et al[1]. Because of the nature of the studies, neither were able to be blinded, but Nijssen et al[3] administered prehydration intravenously and intra-arterial unlike Timal[1] who only did intravenously. Through their statistical analysis, Nijseen et al[3] determined that their subgroups were not significant to suggest a difference with prehydration. Timal et al[1] reported similar findings, with no statistically significant interactions in the subgroups.

Solomon et al[5] was different from the other two studies, as it compared two methods of commonly used prehydration solutions, with saline being the control group. Study population also differed, with inclusion criteria of patients with lower eGFRs. It also specifically looked at contrast with elective coronary or peripheral angiography procedures while the other studies had no preference with procedure characteristics. There were multiple primary outcomes that differed from the other studies. eGFR reduction was looked at as opposed to increase of serum creatinine, in addition to death and renal replacement therapy. Though double blinding was used, there were multiple issues with this study. The study was terminated prematurely, due to inadequate power from decreased enrollment, which could have caused false negatives. There was also a difference in baseline eGFR between the groups, which favored the saline group. A higher dose of sodium chloride was also given than what is typically used when comparing sodium bicarb. Despite these limitations, the study concluded that there was no statistically significant difference in incidence of AKI between sodium bicarb and saline. Though this outcome contributes to the discussion of the necessity of prehydration, it's difficult to incorporate into practice due to its low power. Further studies with adequate power are needed to confirm this finding.

Table 2. Comparison of Statistical Analysis of Studies

	Prehydration Solution	Relative Risk	95% Confidence Interval	P-Value
Study 1	1.4% sodium bicarbonate	1.7	0.5-5.9	0.36
Study 2	0.9% NaCl	1.04	-2.25 - 2.06	0.471
Study 3	1.3% sodium bicarbonate 0.9% sodium chloride	0.91	0.57-1.44	0.78

Conclusion

Overall, withholding administration of prehydration solution before the use of iodinated contrast in patients with known kidney disease had similar outcomes of contrast induced renal injury when compared to the use of sodium bicarbonate or sodium chloride prehydration solution. Although the three studies included in this review did not show a statistically significant difference in the incidence of AKI, the lack of uniformity of primary endpoints and prehydration protocols warrants further investigation into this topic. Further studies should be conducted with more standardized patient populations and a precise consensus of desired endpoint. No longer requiring prehydration protocol has the potential to reduce cost and facility burden with iodinated contrast procedures. While there are still several unanswered questions regarding the specific outcomes of renal injury after contrast use, the risk of CIAKI in patients with decreased kidney function does not appear to be any higher when prehydration is not used.

References

1. Timal RJ, Kooiman J, Sijpkens YWJ, et al. Effect of No Prehydration vs Sodium Bicarbonate Prehydration Prior to Contrast-Enhanced Computed Tomography in the Prevention of Postcontrast Acute Kidney Injury in Adults With Chronic Kidney Disease. *JAMA Intern Med*. 2020;180(4):533-541. doi:10.1001/jamainternmed.2019.7428
2. Rawson JV, Pelletier AL. When to Order Contrast-Enhanced CT. *Am Fam Physician*. 2013;88(5):312-316.
3. Nijssen EC, Rennenberg RJ, Nelemans PJ, et al. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. *The Lancet*. 2017;389(10076):1312-1322. doi:10.1016/S0140-6736(17)30057-0
4. Gupta RK, Bang TJ. Prevention of Contrast-Induced Nephropathy (CIN) in Interventional Radiology Practice. *Semin Interv Radiol*. 2010;27(4):348-359. doi:10.1055/s-0030-1267860
5. Solomon R, Gordon P, Manoukian SV, et al. Randomized Trial of Bicarbonate or Saline Study for the Prevention of Contrast-Induced Nephropathy in Patients with CKD. *Clin J Am Soc Nephrol CJASN*. 2015;10(9):1519-1524. doi:10.2215/CJN.05370514